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INDEX

Fat Absorption Studies in Children: I. Influence of Heat Treatment on Milk on Fat Retention by Premature Infants 207
LARS SÖDERHJELM

Escherichia Coli 55: B 5: 6 in Intestinal Canal of Infants Treated with Lactobacillin Milk ("Lacto-Y-48") 222
A. DUPONT and H. KEISER-NIELSEN

Ectodermal Dysplasia 229
THEODORE JAMES

Effect of Potassium Therapy in Severe Infantile Gastroenteritis 238
NIILO HALLMAN

On the Activity of Chloramphenicol against Haemophilus Influenzae with Special Reference to Influenzal Meningitis 249
J. A. GRÖNROOS

Intravascular Red Cell Aggregation in Newborn Infants with Infections ... 260
T. ARAJÄRVI and H. ZILLIACUS

Intravascular Red Cell Aggregation in Erythroblastosis Foetalis 267
H. ZILLIACUS and T. ARAJÄRVI

Re-Infections with Measles. Familial Immunity Defect 276
ERIK THAMDRUP

A Case of the Hand-Schüller-Christian Disease Treated with Cortisone. (A Discussion of the Primary or Secondary Nature of the Lipoid Deposits) 282
KARL-HENRIK KARLÉN

Alkyl Mercury Poisoning 289
GUNNAR ENGLESON and TORSTEN HERNER

Book Review 295

Almqvist & Wiksells Boktryckeri AB UPPSALA

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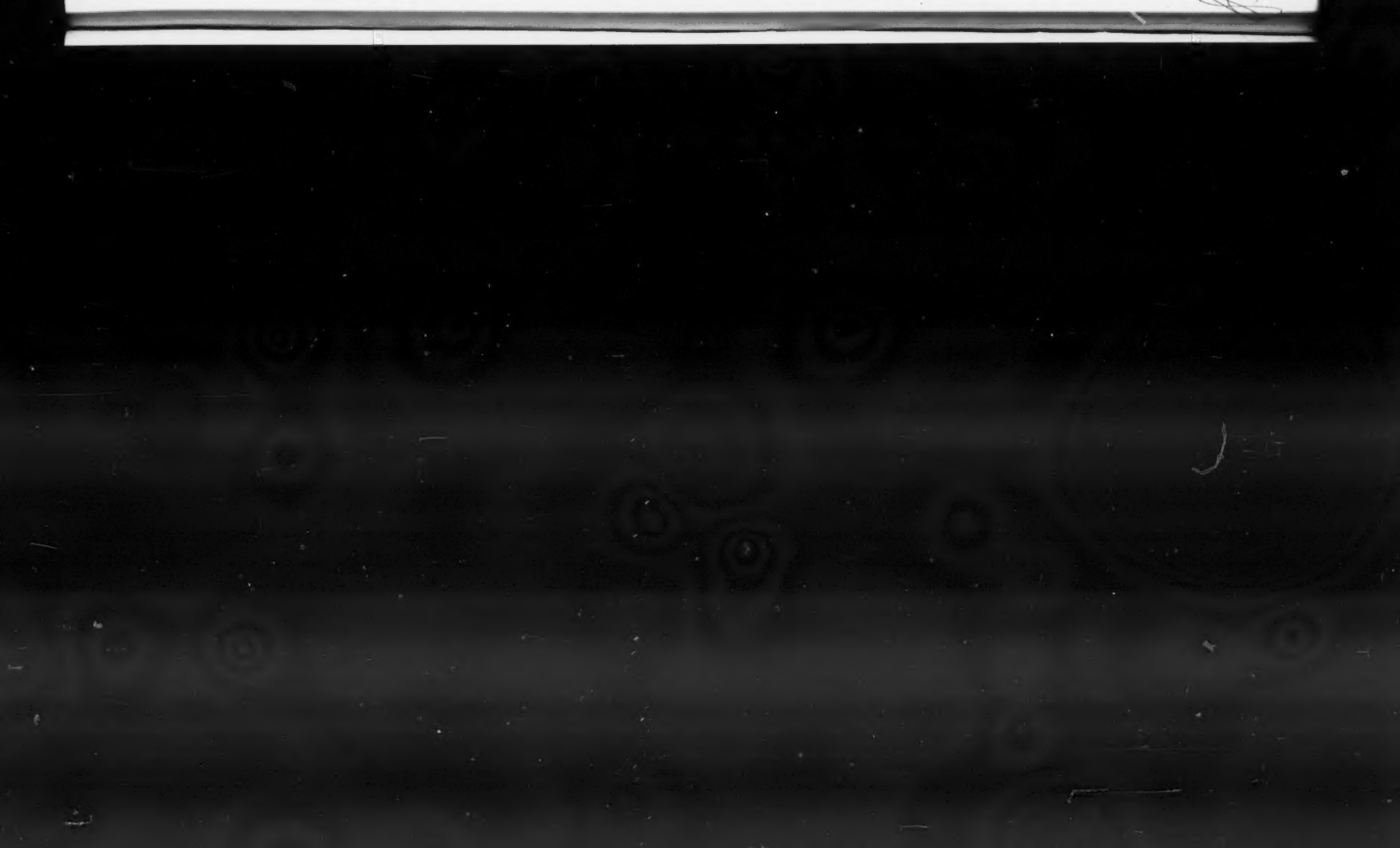

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Fat Absorption Studies in Children. I

Influence of Heat Treatment on Milk on Fat Retention by Premature Infants

by

LARS SÖDERHJELM[1]

Human milk has been considered the food of choice for premature infants. Recently, however, mixtures of cow's milk which have been made poor in fat but rich in protein have been recommended as being especially suitable for this purpose. This change, in part, at least, has been based on the common belief that premature infants do not absorb fat well; hence breast milk, relatively rich in fat, is less desirable, "intended" as it is for full term babies. Actually, however, there is no complete agreement with regard to the superior quality of one or the other type of milk. The purpose of this paper is to report fat balance studies in premature infants who were fed on either human milk or cow's milk.

Historical

A number of workers (UFFELMANN 1881, HOLT 1919, HOLT Jr 1935, GORDON & LEVINE 1937) have reported greater absorption of human milk fat than of cow's milk fat by healthy full term infants. Factors, which have been shown by HOLT and coworkers (1935) to influence the absorption of fat in the healthy full term infant, are age of the child, composition of the milk fat and the mineral content of the milk. In their study, fat absorption was found to increase with increasing age and with

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an increasing proportion of the unsaturated fatty acids in the milk fat. There appeared to be a decreased absorption as the mineral content of the milk increased. The size of the fat globules was of no significance, homogenized milk being absorbed to the same degree. They reported a tolerance of 10 g fat/kg/day by infants 5 to 10 months of age. However, LINDBERG (1917) and REINHOLD (1948) state that when the fat content of breast milk is increased to about 7 per cent, vomiting and gastro-intestinal disturbances result. VAN ESPEN (1946) reports increased vomiting with increased fat content of the breast milk.

RUBNER and LANGSTEIN in 1915 were the first to study the absorption of fat in premature babies fed on breast milk. The fat absorption was a little low in one of their two cases and very poor in the other (39 per cent or the lowest fat absorption so far found in a healthy premature infant). RUBNER and LANGSTEIN seem to have determined the fat absorption indirectly from the metabolism of nitrogen and carbon, weight gain, oxygen consumption etc. It is therefore difficult to evaluate their results. Both infants got large volumes of milk with a high fat content. This was also the case in MUHL's (1926) "Erik O." in the first period. When this infant six weeks later got a more normal volume of milk, the fat absorption was excellent, as in most of the infants studied by her.

GORDON, LEVINE, and coworkers (1937, 1941) found rather poor fat absorption in their carefully performed balance studies. In children weighing more than 2 000 g the fat absorption was satisfactory. GORDON, LEVINE, and coworkers (1940, 1941, 1942, 1947) also found that premature infants fed on breast milk loose more calories in the feces and increase less in weight than infants fed isocaloric amounts of cow's milk formulas with lower fat content and richer in protein and carbohydrate.

FLORI (1941) found excellent fat absorption in eight premature infants, though they got large volumes of breast milk and much fat.

There is a considerable discussion in the literature on the changes produced when human milk is heated, and also on the relative value of raw versus boiled or heated breast milk (LANE-CLAYPON 1913, CATEL 1928, 1938, BERNHEIM-KARRER 1929, BLUME-WESTERBERG 1941). In some instances the fat absorption was studied. CATEL (1938) found a little lower, but still above 80 per cent absorption when the milk was boiled. BLUME-WESTERBERG (1941) did not find that boiling influenced the fat absorption. One of her infants absorbed only 75 per cent of the fat, but received 10 g fat per kg body weight per day.

These earlier investigations thus show good fat absorption with the exception of the cases studied by GORDON and LEVINE and a few other experiments where the infants got large volumes of milk per kg body weight. In view of these contradictory findings, an investigation of fat absorption in premature infants as influenced by the dietary fat from human or cow's milk and with or without heat treatment, was undertaken.

Material and Methods

Data on fat absorption studies on premature infants presented in this paper are the result of two series of experiments, Series A conducted at the University of Uppsala, Sweden and Series B conducted at the University of Texas Medical Branch, Galveston and later continued in Uppsala.

In Series A, at the Children's clinic in Uppsala, the premature infants were given breast milk, either the mother's, in which case it was undiluted and not heated, or pooled breast milk which had been pasteurized at 72° C for 5 minutes or heated for three minutes in boiling water (97° C). All the babies were given daily 10 drops "Guttae AD-vitamini" (Sw. Pharm., about 1 000 units vitamin D in oil). Vitamin C was not given routinely.

In this series, 31 separate fat balances of 4—5 days duration were carried out on eight premature infants, weighing 960—1 960 g. Since the passage of food in premature infants is rather rapid, requiring less than 24 hours usually, it was felt that the collection of the feces over a definite time during which the fat intake was known gave data sufficiently accurate for this study (COOKE and coworkers 1946). Long balance periods, required for older children and adults, do not appear necessary for prematures. Also, a 1 to 2 day adjustment period preliminary to the collection of specimens appears sufficient. The fat content of the milk was determined daily by the GERBER method (Commission d'étude de la matière grasse 1947. Centrifugation with sulfuric acid and amyl alcohol). The fat content of the feces was determined by a method suggested by BLIX and LINDBERG. Essentially it consisted of extraction of max. 5 g wet feces with 100 ml of acid ethanol (96 per cent), first at room temperature, followed by heating on the water bath for 5 minutes. The extract was filtered hot and the fecal residue re-extracted three times with 25 ml of 96 per cent ethanol. The combined filtrates were concentrated in vacuum at 37—40° C to about 50 ml and then shaken with 100 ml of ethyl ether and 100 ml of distilled water. The ether extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness.

In Series B, conducted at the University of Texas Medical Branch and later continued in Uppsala, the premature infants were given either human milk or cow's milk. The effects of freezing or heating the milks to various temperatures on the fat absorption were determined.

In this series 67 separate balance studies were conducted on 24 premature infants, weighing 1 080 to 2 220 grams. The periods were of 4 to 7 days duration. The infants were kept in incubators and fed 140—190 ml milk/kg/day. A polyvitamin mixture was given daily to most of the infants at the beginning of the second week of life. The following

effects in the treatment of the milks were studied: 1. Human milk, untreated, frozen[1], pasteurized for 20 minutes at 62° C, heated on a boiling water bath for 20 minutes at 97° C, or heated in an open pan for 3 minutes at 100° C; 2. Whole cow's milk, pasteurized for 20 minutes at 62° C (homogenized in 2 instances), or boiled in an open pan at 100° C for various lengths of time. Carmine and charcoal were used to mark the beginning and end of each period. It was found that the rate of passage of these markers in the premature was the same. Charcoal, however, sometimes causes slight irritation of the bowel and its use was later discarded and carmine used instead. As was pointed out by MACY (1939) the stools of children receiving carmine might be somewhat looser than otherwise. The dosage used by her was 0.2—0.3 g to children 7 to 11 years old. In the present study 0.05—0.10 g carmine was given. In certain cases this caused slightly loose stools at the passage of the marker. (In similar study EDMUNDS (1950) gave more than 0.4 g of carmine to infants, which almost always will produce diarrhea).

The fat content of the milk was determined daily using the MOJONNIER method (STEAGALL 1945) with slight modification. The fat content of the wet feces was determined by a MOJONNIER extraction procedure described by SÖDERHJELM and SÖDERHJELM (1949).

Discussion of the methods used

Careful investigations by GORDON, LEVINE, and coworkers (1940) showed a maximum loss of 5 per cent of the milk given to premature babies. This was due to regurgitated milk and milk left in bottles, tubes, and the mouths of the babies.

In our experiments smaller volumes of milk were used and regurgitation was rare; this was estimated and deducted from the milk given. The losses of milk in the procedures carried out in these investigations were found to be maximum 2.5 per cent. This small percentage would influence the figures of fat absorption only slightly.

The most difficult problem is the complete collection of the stools. In cellulose or paper there is too much lipoid material to allow collection of the feces on paper. TIDWELL, HOLT *et al.* (1935) extracted the diaper with the stools and deducted 0.5 g of fat for each diaper; this is a high figure compared to the fat content of the feces and therefore the accuracy is decreased.

Some of the infants in my experiments were placed on plastic sheets. The results were slightly different from those with common cotton diapers. Seven infants were studied in this way and the fat absorption

[1] Pooled milk, autoclaved at 114° C, then frozen 2—6 mo. or pooled milk frozen 1—2 mo., heated 5 min. 72° C.

Table 1.

Comparison of percentage total fat extracted from wet feces by methods of Söderhjelm-Söderhjelm and Blix-Lindberg.

Specimen	Söderhjelm-Söderhjelm	Blix-Lindberg
1	6.96	6.59
2	6.12	6.19
3	6.85	6.43
4	0.54	1.06
5	0.69	1.17
6	5.99	5.92
7	4.88	4.87

on cotton diapers was 85 per cent, on plastic sheets 81 per cent on an average.

In order to find out how much is lost in the diapers, feces of known fat content were spread out on diapers and the losses in a repeated collection determined. In this procedure 4 to 20 per cent of the fat was lost. The feces had been mixed with water and were considerably thinner than stools of normal breast fed infants. The greater losses were found in the loosest stools when small amounts of feces were spread out. In the present study all infants with diarrhea were excluded.

The methods used here for the determination of fat give the total fat of the feces, not only the saponifiable fat. Thus the possible losses in the diapers are at least partly compensated.

A comparison of the *Mojonnier* flask-method of extracting fecal fat with the procedure suggested by BLIX and LINDBERG (used in Series A) was made to see whether or not the results of the absorption studies in the two series were comparable. As noted in Table 1 the average of duplicate determinations made on the same specimens by the two methods agree very closely, the greatest difference being slightly less than 5 per cent except when the amount of fat was extremely low.

The balance studies in this investigation thus are not "exact," a very difficult achievement. But the possible losses are not great and do not considerably influence the conclusions drawn. In the tables the figures found are given, in the conclusive table on fat absorption a loss of 5 per cent of the fat of the food and 10 per cent of the fat of the feces is postulated.

Results

The results of the fat balance studies in Series A are given in Table 2. It is evident that absorption of fat from human milk

Table 2.

Series A — Details relating to the absorption of fat from breast milk by premature infants.

Case	Sex	Birth Weight g	Period days	Age days	Weight g	Treatment of Milk	g fat/kg/day		Absorbed fat per cent	Avg. gain g/day
							intake	output		
1	F	1 700	5	18	1 740	raw	4.9	0.6	87	14
			4	25	1 850	raw	4.4	0.5	89	15
2	M	1 190	5	13	990	raw	3.9	0.1	98	14
			4	20	1 090	raw	4.4	0.2	96	10
3	M	1 000	5	40	1 280	raw & heated [1]	5.3	0.3	93	17
			4	47	1 390	raw	5.0	0.04	99	13
			5	60	1 550	raw	4.8	0.1	98	5
			5	75	1 670	heated	4.5	0.1	99	25
			5	82	1 770	heated	4.9	0.1	98	2
4	F	1 160	5	26	1 120	raw & heated	5.2	0.9	83	10
			4	33	1 160	raw	5.2	0.9	83	3
			5	45	1 230	raw	6.0	0.9	85	12
			5	60	1 390	heated	4.9	0.1	97	12
			5	67	1 500	heated	4.8	0.7	85	7
			4	74	1 610	raw	6.0	0.2	97	3
5	F	1 160	4	29	1 300	heated	4.1	0.3	93	16
			4	36	1 390	heated	4.0	0.04	99	26
			5	43	1 570	heated	3.3	0.4	88	17
			4	51	1 700	heated	4.2	0.3	92	23
6	F	1 160	4	6	960	raw & heated	3.3	0.3	92	13
			5	13	1 040	raw	6.0	1.3	78	15
			4	21	1 150	raw	6.4	0.4	94	7
			5	27	1 250	raw	5.5	1.1	81	12
			5	34	1 360	raw	6.1	1.2	80	10
			5	42	1 480	raw	5.8	0.4	93	22
			4	54	1 700	raw	4.4	0.1	97	17
			5	63	1 830	raw	5.0	0.3	95	20
7	M	1 940	4	18	1 850	raw & heated	5.1	0.4	93	3
			5	27	1 960	raw & heated	5.3	0.5	90	17
8	F	1 740	4	11	1 600	raw	4.1	0.3	93	15
			5	15	1 660	raw	5.1	0.5	90	20

[1] In this and the following experiments »heated» = heated for 3 minutes at 97° C or 72° C for 5 min.

Table 3.

Series B — Details relating to the absorption of fat from breast milk by premature infants.

[1] In this and the following experiments »heated« — heated for 3 minutes at 97° C or 72° C for 5 min.

Table 3.

Series B — Details relating to the absorption of fat from breast milk by premature infants.

Case	Sex	Birth Weight g	Period days	Age days	Weight g	Treatment of Milk	g fat/kg/day		Absorbed fat per cent	Avg. gain g/day
							intake	output		
9	M	2 170	3	8	2 060	62° C 20 min.	4.2	0.2	94	37
			5	11	2 170	62° C 20 »	4.3	0.1	97	16
			5	17	2 310	97° C 20 »	4.5	0.1	99	20
			4	23	2 460	97° C 20 »	5.4	0.1	97	12
			4	27	2 510	97° C 40 »	6.0	0.1	98	35
10	M	1 880	3	8	1 750	97° C 20 min.	3.6	0.5	86	27
11	M	1 710	5	6	1 550	62° C 20 min.	3.3	0.3	92	6
			5	12	1 600	62° C 20 »	4.1	0.7	84	24
			5	21	1 850	97° C 20 »	4.7	0.6	87	12
			5	27	1 950	97° C 20 » / 100° C 3 »	5.4	0.6	89	24
			5	33	2 100	100° C 3 »	4.8	0.3	94	40
14	F	1 200	5	34	1 730	62° C 20 min. / 100° C 3 »	5.7	0.3	95	42
18	M	1 970	4	18	2 040	62° C 20 min. / 97° C 20 »	3.8	1.1	71	18
35	F	1 600	5	23	1 570	untreated	7.4	1.1	85	18
			5	33	1 760	»	7.0	0.8	89	20
37	F	1 140	6	35	1 520	untreated	3.9	0.4	91	15
			5	45	1 650	»	5.0	0.4	93	10
38	M	1 710	5	22	1 700	97° C 3 min.	4.3	0.3	93	22
			4	29	1 860	97° C 3 »	3.7	0.2	94	22
41	F	1 860	5	8	1 650	97° C 3 min.	5.9	1.5	76	28
			5	13	1 790	untreated	6.2	1.3	79	22
			5	18	1 910	»	5.6	0.6	90	18

Table 4.

Series B — Details relating to the absorption of fat by premature infants fed frozen breast milk.

Case	Sex	Birth Weight g	Period days	Age days	Weight g	Treatment of Milk	g fat/kg/day		Absorbed fat per cent	Avg. gain g/day
							intake	output		
20	F	1 910	6	10	1 690	frozen[1]	4.8	1.7	65	12
			6	17	1 810	» [1]	6.3	1.2	81	16
21	F	1 930	5	12	1 870	100° C 3 min.	7.1	0.4	94	12
			6	17	1 930	100° C 3 »	4.5	0.5	90	27
			5	24	2 090	frozen[1]	6.4	0.3	96	42
22	F	2 055	5	11	2 030	frozen[1]	4.2	0.5	89	6
24	M	1 765	5	4	1 630	frozen[1]	2.6	0.2	87	−6
30	M	1 350	6	15	1 370	frozen[2]	4.6	0.9	81	−2
			6	23	1 380	72° C 5 min.	4.2	0.4	91	12
			6	29	1 450	72° C 5 »	3.5	0.3	90	10
			6	37	1 550	frozen[2]	5.0	0.3	94	15
			6	43	1 610	» [2]	5.3	0.3	94	15
			6	52	1 740	72° C 5 min.	5.1	0.2	96	18
31	M	1 920	6	10	1 660	72° C 5 min.	4.6	0.6	86	5
			6	16	1 700	72° C 5 »	4.3	0.3	92	10
			6	24	1 770	frozen[2]	5.1	0.3	95	8
			6	30	1 840	frozen[2]	5.5	0.2	96	20
32	F	1 200	6	23	1 080	72° C 5 min.	5.3	0.7	86	12
			6	32	1 200	frozen[2]	5.9	0.9	84	12
33	F	1 690	5	10	1 560	72° C 5 min.	4.2	0.3	93	2
			5	17	1 600	frozen[2]	5.1	0.8	84	15
34	F	1 400	6	30	1 400	74° C 5 min.	4.5	0.6	88	15
			6	40	1 540	frozen[2]	5.4	0.6	89	13

[1] Pooled milk, autoclaved 114° C, frozen 2—6 months.
[2] » » , frozen 1—2 months; heated 5 min. 72° C.

Table 5.

Series B — Details relating to the effect of heat treatment of cow's milk on absorption

Table 5.

Series B — Details relating to the effect of heat treatment of cow's milk on absorption of fat by premature infants.

Case	Sex	Birth Weight g	Period days	Age days	Weight g	Treatment of Milk	g fat/kg/day		Absorbed fat per cent	Avg. gain g/day
							intake	output		
12	F	1 820	4	17	2 080	62° C 20 min.	5.7	2.2	61	7
			5	23	2 170	62° C 20 » H[1] / 97° C 20 »	5.5	2.0	63	24
			4	31	2 400	62° C 20 »	5.8	2.2	62	32
			5	37	2 585	62° C 20 » / 97° C 20 »	7.8	2.3	70	31
13	M	2 210	5	14	2 220	62° C 20 min. / 97° C 20 » H[1]	4.2	1.1	73	20
			4	22	2 390	62° C 20 »	5.1	1.3	74	40
			5	28	2 640	62° C 20 » / 97° C 20 »	6.7	1.6	75	38
14	F	1 200	7	40	1 940	100° C 3 min.	5.9	0.8	86	17
			7	48	2 050	100° C 6 »	6.0	1.0	84	34
15	M	1 300	7	8	1 220	100° C 3 min.	4.0	0.9	77	8
			7	16	1 320	100° C 6 »	4.0	1.5	63	18
			7	24	1 440	100° C 30 »	4.6	1.5	61	28
			7	31	1 640	100° C 30 »	4.6	1.9	59	24
			7	39	1 810	100° C 3 »	4.5	2.0	56	20
16	M	1 590	7	10	1 550	100° C 3 min.	4.2	0.7	84	6
			7	18	1 640	100° C 6 »	5.0	0.7	85	29
			7	26	1 840	100° C 30 »	5.4	0.7	87	36
			7	33	2 090	100° C 30 »	5.6	0.9	85	19
			7	41	2 260	100° C 3 »	5.3	0.7	87	24
17	F	1 370	7	12	1 470	100° C 30 min.	3.8	1.4	62	22
			6	19	1 625	100° C 30 »	4.6	1.8	61	18
			7	27	1 770	100° C 3 »	4.4	1.9	57	13

[1] Homogenized.

in this series was excellent. Heating the milk to 72° C for 5 minutes or 97° C for 3 minutes did not influence the degree of absorption. In the weight range of these infants who received 3.3 to 6.4 g fat/kg/day representing 30 to 60 cal./kg, there was no significant difference in the degree of absorption of the fat. The mean absorption for the group was 92 per cent which is as good as for full term infants. The weight gains during the individual periods were not directly related to the amount of fat absorbed. The average increase in weight was almost 12 g per day in these infants.

The results of the fat balance studies in Series B using breast milk which had various heat treatments comparable to those in Series A are given in Table 3.

With one exception, case 18 (Table 3), fat absorption with intakes of 2.6 to 7.4 g/kg/day was as good as in the infants in Series A, even though heat treatment was more severe, 20 minutes at 62° C or 97° C or a double heat treatment. The average daily increase in weight was about twice that of those infants presented in Table 2, but this difference is readily explained on the size of the subjects.

The influence of freezing and storage of breast milk on fat absorption is indicated by data presented in Table 4 and Figure 1. It is apparent that freezing does not decrease the degree of absorption. In only one instance (an early period in case 20) the absorption was poor, yet when the same infant weighed 120 g more with a greater fat intake the per cent fat absorption was increased. The frozen breast milk which represents pooled milk which has been autoclaved at 114° C before freezing and subjected to an additional heat treatment or pasteurization before use, appears to be just as satisfactory in regard to fat absorption by premature infants as the fresh milk heated for 5 minutes at 72° C before use. The average daily increase in weight was comparable to the previous groups mentioned in view of the size of the infants.

The premature infants who were given cow's milk pasteurized or heated for various intervals with intakes of fat 3.8 to 7.8 g/kg/day retained fat to a considerably lesser extent than the infants fed breast milk (Table 5). The retention of fat in these 22 ex-

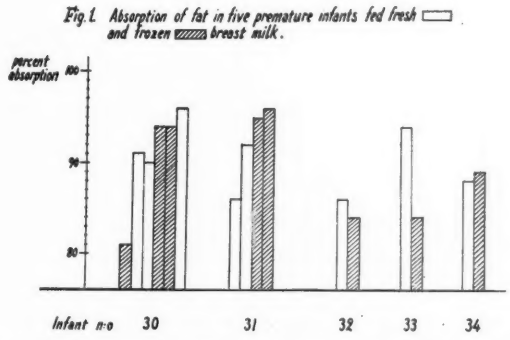

Fig. 1. Fat absorption in five premature infants fed fresh and frozen breast milk.

perimental periods on six different premature infants was about 71 per cent, on the average, and the type of heat treatment did not alter the retention. The average gain in weight was 22 g per day which again was average for the size of the infants.

Discussion

Absorption of fat from both breast milk and cow's milk by premature infants seems remarkably good, when the amounts given are in the range of 3 to 7 g/kg/day. Even small premature infants seem to retain fat well. Nine infants weighing less than 1 500 g studied over a period equivalent to 117 days, absorbed 91 per cent of the fat from breast milk. The average intake was 5.4 g (3.3 to 7.1 g/kg/day). The degree of absorption was not altered by the treatment given the milk (pasteurized, frozen or heated). With cow's milk fat, absorption was about 66 per cent when the fat was given at a level of about 4 g/kg/day but only two infants were studied for a period equivalent to 28 days. The degree of absorption of fat from cow's milk by the small premature infants is much different from the larger premature infants. Both smaller and larger premature infants, however, retain fat from breast milk with greater facility than from cow's milk.

Gain in weight usually is used as a criterion of effectiveness for feeding the premature infant. Difficulty in fat absorption

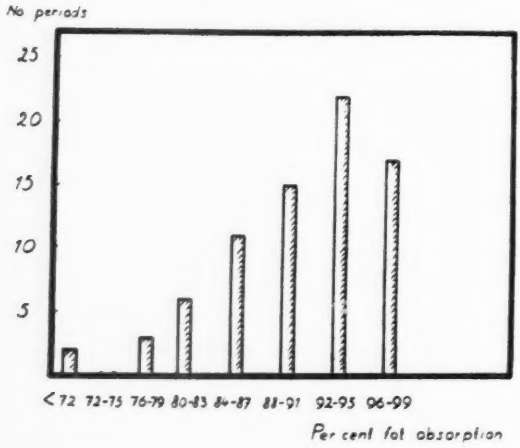

Fig. 2. Fat absorption in 26 premature infants fed breast milk in 76 balance periods.

by prematures has been emphasized by different workers as one of the important problems to be met in proper premature infant feeding. FORD (1949), however, reported satisfactory weight gain in prematures maintained on breast milk. ÖBERG and ÅGREN, in a personal communication, stated they found no difference in the weight gain of premature infants fed isocalorically on breast milk or formulas richer in carbohydrate and protein. If it is true that premature infants actually do increase in weight more rapidly when fed on diets low in fat, it cannot be stated that this is attributable to the inability of the premature infant to absorb fat satisfactorily. The data herein reported show that most premature infants retain breast milk fat practically as efficiently as has been reported for full term infants.

The absorption of breast milk was studied in 26 premature infants in 76 periods of 3—6 days duration. In four infants and five periods the fat absorption was below 80 per cent, in 31 periods 80—90 per cent, and in 40 periods above 90 per cent (Fig. 2).

If correction is made for the possible loss of 5 per cent of the fat of the milk and 10 per cent of the fat of the feces the following

Table 6.

	no. periods	< 80 %	80—90 %	> 90 %	Median %
found.....	76	5	31	40	92
"corrected" .	76	9	28	39	89

figures (Table 6) are deduced: below 80 per cent absorption in 9 periods, 80—90 per cent in 28 periods, and above 90 per cent in 39 periods.

Summary

A total of 98 fat balance studies varying from 3 to 7 days duration was made on 32 premature infants weighing at the beginning of the studies from 960 to 2 220 g. The fat content of diet varied from 2.6 to 7.8 g kg day and was supplied from breast milk, raw, frozen or heated at various temperatures for different intervals of time or from cow's milk, pasteurized, or subjected to heating at various temperatures for different periods. It is concluded that prematures retain breast milk fat to a remarkably high degree even though the breast milk has been frozen or subjected to various heat treatments. Premature infants do not retain fat from cow's milk as efficiently as they do human milk fat. The nature of the heat treatment of cow's milk did not influence the degree of retention.

Études sur l'absorption des graisses chez les enfants. I. Influence du traitement du lait par la chaleur sur la rétention des graisses chez les prématurés.

L'auteur a étudié chez 32 prématurés pesant au début de l'expérimentation de 960 à 2 200 g, 98 bilans de l'absorption-excrétion des graisses pendant un laps de temps variant de 3 à 7 jours. Le contenu en graisses du régime variait entre 2,6 et 7,8 grammes par kg et par jour, et provenait soit de lait de mère cru, réfrigéré et réchauffé à des températures variables et à des intervalles de temps différents, soit de lait de vache pasteurisé ou soumis à des écarts de température variés dans le temps. L'auteur a pu conclure que les prématurés absorbent les graisses du lait de mère dans une proportion remarquablement élevée, même quand celui-ci a été refroidi ou chauffé. Il n'en est pas de même par contre, des graisses données sous forme de lait de vache, qui sont en effet retenues avec moins de profit. Le traitement par la chaleur du lait de vache n'influence pas son degré d'absorption.

Studien über Fettabsorption bei Kindern: I. Der Einfluss mit Erhitzung behandelter Milch auf die Fettretention bei frühgeborenen Säuglingen.

Insgesamt wurden 98 Fettbilanzstudien von 3 bis 7 Tage Dauer an 32 frühgeborenen Säuglingen gemacht, deren Gewicht bei Beginn der Untersuchungen 960 bis 2 200 g betrug. Der Fettgehalt der Nahrung variierte zwischen 2,6 und 7,8 g/kg/Tag und wurde geliefert durch Brustmilch, roh, gefroren oder erhitzt bei verschiedenen Temperaturen während verschiedener Zeiträume, oder durch Kuhmilch, welche pasteurisiert oder bei verschiedenen Temperaturen während verschiedener Perioden erhitzt worden war. Der Verfasser zieht den Schluss, dass Frühgeborene Brustmilchfett in bemerkenswert hohem Grade retinieren, auch wenn die Brustmilch gefroren oder in verschiedener Weise erhitzt worden ist. Frühgeborene Säuglinge behalten Fett von Kuhmilch nicht so gut wie menschliches Milchfett. Die Art der Hitzebehandllng der Kuhmilch hatte keinen Einfluss áuf den Grad der Retention.

Estudios sobre la absorción de grasa en los niños. I. Influencia del calentamiento de la leche sobre la retención de grasa en los prematuros.

En 32 prematuros cuyo peso al principio de la experiencia oscilaba entre 960 y 2 200 g se hicieron un total de 98 determinaciones de balance de grasas de duración de 3 a 7 días. La grasa contenida en la dieta variaba de 2,6 a 7,8 g por kilo y día y era aportada en forma de leche materna, cruda, helada o calentada a varias temperaturas en intervalos de tiempo diferente, o bien leche de vaca pasteurizada o sometida también a calentamiento a temperaturas diversas. De las experiencias se deduce que los prematuros retienen la grasa de la leche materna con un porcentaje muy elevado, aunque esta leche haya sido helada o sometida a diversas temperaturas; en cambio los prematuros no requieren la grasa de la leche de vaca de un modo tan eficiente como la de la leche humana. La influencia del calentamiento de la leche de vaca no es importante sobre el grado de retención de grasa.

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Escherichia Coli 55: B 5: 6 in Intestinal Canal of Infants Treated with Lactobacillin Milk ("Lacto-Y-48")

by

A. DUPONT and H. KEISER-NIELSEN

In recent years colibacilli have been demonstrated as the presumable cause of endemic enteritis in infants (1, 3, 4, 5, 6, 7, 8, 9, 17, 18). In Denmark, bacteriological studies on E. coli 55: B5 and E. coli 111: B4 have been published by KAUFFMANN and DUPONT (1950) from Statens Seruminstitut (10).

During the past year a group of children, including some from two children's homes, have been admitted to a Copenhagen County Hospital for severe gastro-enteritis. Culture of the feces yielded E. coli 55: B5: 6. As a rule these children were merely moderately exhausted. In some cases these strains of colibacilli persisted in the feces for several weeks after clinical recovery. In some cases the presence of these strains was demonstrable even after a short period of streptomycin therapy. The risk of these children's transmitting the infection seemed to make their discharge unwise. This would be particularly true for those patients from the children's homes. The question then arose whether it might not be practicable to eliminate these colibacilli by some physiological process rather than by trying a protracted treatment with antibiotics.

With this end in mind some experiments with lactobacilli treatment were made. A culture of "Lacto-Y-48", isolated by Professor MØLLGAARD from pig feces in the National Research Institute on Animal Husbandry, Copenhagen, was employed. This

culture, now available on the market, is grown in a medium of whole milk, and distributed by the Danish Dairy Laboratory, Ltd.

The theoretical basis for this therapy may be found in numerous reports in the literature, according to which the intestinal flora may be altered to a lesser or higher degree by the administration of various acidophil bacteria, together with lactose, if required. Among the various reports of this kind published in Denmark, mention may be made of the work by ORLA-JENSEN and WINTHER (1934) (16), covering various acidophil strains, MEJLBO and NYGART (1939) (12), by MEJLBO, NYGART and PLUM (1941) (13) and by ORLA-JENSEN, OLSEN and GEILL (1945) (15). For a comprehensive list of references and for a theoretical treatment of this subject, the reader is referred to the dissertation by ERIK OLSEN (1949) (14). The results reported, as a rule, have been good, though far from uniform.

Patient Material

The present material comprises 11 infants under 6 months, who all presented E. coli 55 in the feces. After symptom-free periods of varying lengths, they were treated with large amounts of "Lacto-Y-48". No other changes were made in their diet (usual milk mixtures). As a rule, one-half of the usual daily amount of the milk in the mixture was given in the form of Y-milk, though sometimes the amount was greater. According to the present experiences, this dosage is sufficient, and in infants at any rate — it should hardly be increased further. Frequently, the use of saccharine as a sweetening was required.

All the specimens of feces were bacteriologically examined for E. coli: 55: B5: 6 and E. coli 111: B4 in the way usually employed in routine examination, namely: from a large primary Conradi-Drigalski plate a mass and at least 10 single colonies were picked out for slide agglutination tests in drops of OB serum produced with the two coli types (and also in saline whenever there was any rough agglutination). The B5-positive colonies isolated in this way were stored for additional examinations:

1. Complete fermentation tests.
2. O agglutination, with titration of a broth culture, boiled for 1 hour, in E. coli 55 O serum.
3. H agglutination in an H6 serum after the strain has been rendered motile and then killed with formalin.

From the above-mentioned cases, altogether 102 coli strains have been isolated, all with the characteristics of E. coli 55: B5: 6.

However, as no definite result was obtained in the cases of the first 7 children, the glucose added to the milk was replaced by lactose (as a cultural medium for the lactobacilli in the intestine). Various papers have been published — e. g., by BJØRNEBOE (1937) (2) — according to which the mere addition of lactose instead of glucose to the milk mixture lowers the pH of the feces considerably and makes a distinct change in appearance. Lactose was added in large amounts making the total lactose content of the milk about 8 %, as it has been stated that in infants the lactase can split a part of the lactose before it reaches the intestine.

In 3 cases, for a time, 10 % lactose was tried, but this seemed not to be quite tolerable.

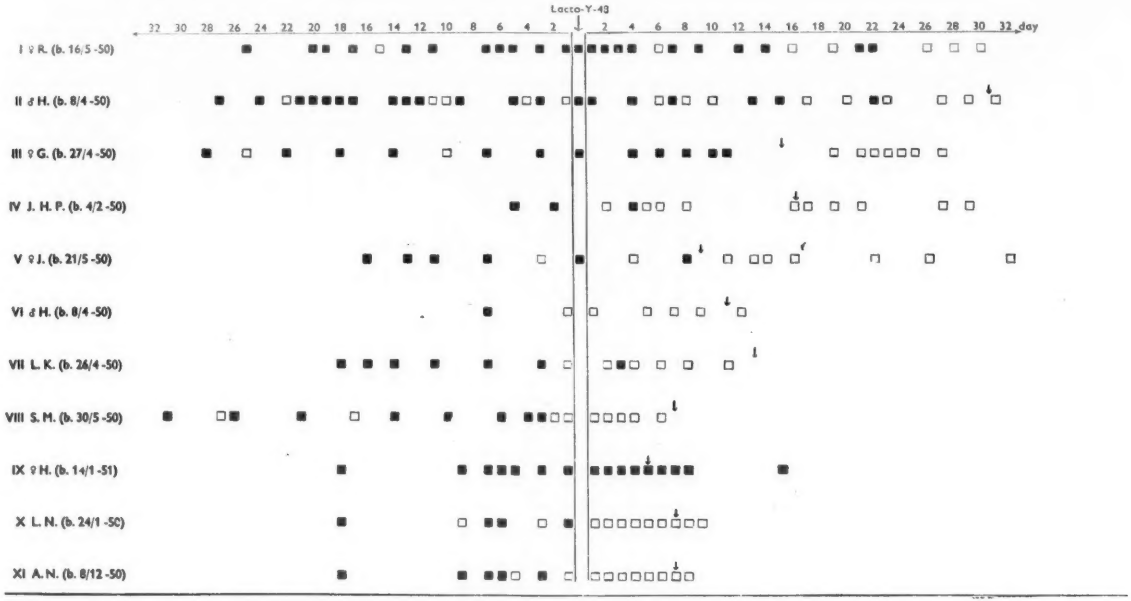
The stools in which the hydrogen ion concentration was to be determined were kept rolled up in the diaper and were examined within a few hours after evacuation. The stools were stirred with a small quantity of water free from carbon dioxide before measurement with a potentiometer. Control duplicate tests with a considerable amount of water as well as with a small amount, and with short and long storage times, conveyed the impression that the results obtained in these determinations were reliable. The results always agreed with those obtained with indicator paper.

In the 4 children who were given lactose, the hydrogen ion concentration of the feces was unaffected in 1 (pH about 7.0—8.0), while in the remaining 3 children the results were uncertain and variable (the lowest values being 5.14, 5.75 and 5.10, respectively). Once, however, the result was 7.89, after 5 days of treatment. This was on the day following a result of pH = 5.10. No definite effect on the appearance of the feces was noticeable. As a rule, the children took the Y-milk mixtures rather well, but sometimes it seemed as if they had an increased tendency to regurgitation, and were not thriving too well. However, the present material is much too limited to allow any definite statement in this respect.

As it was stated by MEJLBO (1939) that it is just the production of a marked decrease in the fecal pH to about 5.0 or lower which is the effective factor in the eradication of "isocolibacillosis" in suckling calves, we found that the results obtained by us did not encourage us to make use of this treatment to more children.

The results obtained from the fecal cultures are presented schematically in the Table. (In this tabulation, close consideration has been given to the time for the evacuation of the first as well as the last samples of feces in relation to the date of the institution of the Y milk therapy.)

From the Table it will be noted that in 4 cases (VI, VII, VIII and XI) treatment was commenced about the same time as the fecal cultures



Explanation of signs: ■ = + E. coli 55.
□ = no E. coli 55.
↓ = discont. of Lacto-Y-48.

The cases VIII, IX, X and XI were treated with Lacto-Y-48 and Lactose.

Schematic Survey of 11 Infants presenting E. coli 55; B5; 6 in their Feces and treated with Lactobacillin Milk (Lacto-Y-48).

were, or were becoming negative. In these cases it cannot be decided how much the treatment has influenced the result. Among the remaining 7 cases, no effect of the treatment was noticeable in the 4 (I, II, III and IX), in 2 cases (IV and V) there may be some effect, and only in one case (X), E. coli 55 disappeared from the feces simultaneously with the institution of the treatment.

Conclusion and Summary

11 infants, who after apparent clinical recovery, persisted in discharging E. coli 55: B5: 6 in their feces, were treated with lactobacillin milk. Of these children 4 were given considerable amounts of lactose in their milk.

Only 3 cases may properly be said to have shown a good therapeutic result, and on a whole the results of this experiment are negative.

Whether the results in these cases justify further therapeutical experiments will presumably depend on the results obtained in a larger number of cases treated with antibiotics. So far, antibiotics also have given highly variable results in the eradication of special types of E. coli from the intestinal canal, due either to variations in resistance or to reinfections.

Escherichia Coli 55: B5: 6 dans le tractus intestinal d'enfants traités par le "lactobacillin milk" (Lacto-Y-48).

11 enfants qui, après leur apparents guérison clinique, présentaient toujours dans leurs selles du E. Coli 55: B5: 6, furent traités par le "lactobacillin milk". Quatre de ceux-ci recevaient en outre un excès considérable de lactose dans leur lait. 3 cas seulement parmi les 11 permettent de conclure à une bonne action thérapeutique. C'est pourquoi on doit conclure à un échec relatif, dans la série envisagée. Des résultats obtenus dans un plus grand nombre de cas traités par les antibiotiques dépendra la valeur des tests proposés et l'intérêt qu'il y aurait ou non de poursuivre de plus amples recherches thérapeutiques dans cette voie. Ceci est d'autant plus important que le traitement antibiotique de types spéciaux de bacilles E. Coli isolés du tractus intestinal a donné des résultats des plus variables. Ceci peut être du aux variations individuelles de résistance vis à vis des germes ou aux réinfections.

Behandlung der Escherichia coli 55: B5: 6 im Darmkanal von Säuglingen mit Lactobazillusmilch ("Lacto-Y-48").

Elf Säuglingen, welche nach anscheinender Genesung weiterhin Eschericia coli 55: B5: 6 im Stuhl absonderten, wurden mit Lactobazillusmilch behandelt. 4 von diesen Kindern wurden weiterhin namhafte

Laktosemengen mit der Milch eingegeben. Wenn man die Ergebnisse dieser Gruppe betrachtet, so kann man nur von 3 Fällen wirklich sagen, dass sie einen guten therapeutischen Erfolg aufweisen; im übrigen ist dieser Versuch negativ ausgefallen. Ob die in diesen Fällen durchgeführten Proben weitere therapeutische Experimente in entsprechenden Fällen rechtfertigen, wird wahrscheinlich von den Behandlungsergebnissen mit Antibiotika bei einer grösseren Anzahl von Fällen abhängig sein; die Letzteren haben bis jetzt auch sehr schwankende Ergebnisse in bezug auf die Ausrottung besonderer Arten von Eschericia coli aus dem Darmkanal gezeigt (sei dies der verschiedenen Widerstandskraft oder einer Wiederansteckung zu verdanken).

Escheriquia coli 55: B5: 6 en el tracto intestinal de niños tratados con leche con bacilos lácticos ("lacto-Y-48").

Once niños los cuales tras recuperación clínica eliminaban en sus deposiciones e. coli 55: b 5: 6 fueron tratados con leche con lactobacilina. De estos niños 4 habían recibido considerables cantidades de lactosa en la leche. Los resultados obtenidos con este material prueban que en solo 3 casos puede hablarse propiamente de un buen resultado, el resto de la experiencia es más bien negativa. Toda vez que las experiencias en estos casos justifica otros experimentos terapéuticos en casos análogos posiblemente dependientes de los resultados obtenidos en un gran número de casos tratados con antibióticos los cuales han dado grandes variaciones en los resultados en lo que concierne a la desaparición de tipos especiales de e. coli del tracto intestinal (toda vez que ello puede ser debido a variaciones de la resistencia o reinfecciones).

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Ectodermal Dysplasia

by

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This syndrome, while it is uncommon, is not to be looked upon as a rarity. The two case reports of this paper were observed within four months of each other. In 1848 THURNAM and WILLIAMS gave the first descriptions of this peculiar condition, the first reporting the anhydrotic type in the male and the second reporting the same type in the female. Since then cases have been reported from various parts of the world and these cases vary considerably in the manifestations described, from the fully-developed ectodermal dysplasia at one extreme to minor variations of dental dysplasia or aplasia, or hypotrichosis only, at the other. The vast majority of cases have been males.

WEECH (1929) endeavoured to show by a study of the family histories of cases in the literature that transmission of the defect as a non-sex-linked dominant may occur, and in other cases that it may be sex-linked. He thought of the possibility of a mendelian non-sex-linked transmission in which event both males and females should be capable of passing on the defect and normal progeny be unable to transmit. In the sex-linked type the inheritance of the syndrome in the male is through the female and is analogous to that of hemophilia and colour-blindness, carried by the female and expressed in the male, and PRETO'S (1948) account of 7 cases of congenital ectodermal defect in one family is interesting in this respect. All the affected members of the family were male, there being 1 in the first, 1 in the third and 5 in the fourth generation, clearly showing transmission to males through the female.

However, WEECH'S 2 cases were in themselves different in that his case 1 was of the anhydrotic type, as he called it, and his case 2 had normal sweat glands, yet the family history of his case 2 strongly suggested that the defects had been transmitted *through the male*. He regarded GOECKERMANN'S case (1920, cit. COCKAYNE 1933), a female of the anhy-

drotic type, as of great importance in that it weakened the contention that anhydrosis is a characteristic of sex-linked inheritance and GUILDFORD'S case (cit. COCKAYNE 1933) also tends to confuse the issue, for GUILDFORD had a patient, an anhydrotic male, whose mother was the normal daughter of a woman who lacked both hair and teeth.

WEECH put forward the idea that characteristic features identical in the 2 types could be explained by an assumption that totally different genes may be responsible for identical characteristics and that this could account for the anomalies of inheritance by "principal genes" and "mutant genes" concerned, to a greater or less degree, with the same anomaly; e. g. if the gene or genes involved with dental dysplasia can be transmitted alone or be recessive, dentition would probably be normal; but if the same type of mutant gene be present in both parents the progeny of both sexes might show the dental defect in the absence of anhydrosis. An adequate explanation for anhydrosis in the female was not available at the time (1929).

BRAIN (1937) at a meeting of the Royal Society of Medicine presented a boy of 12 years, who, at 6 years of age after contracting bronchopneumonia which was followed by pertussis, lost all the hair of his head. New hair grew later but much of it continued to come away in the comb. This boy's skin was not abnormally dry nor did he complain in warm surroundings. He cut his first teeth at 9 months and the teeth then were pointed. The boy's father had 1 dystrophic nail which incompletely covered the nail bed. A male sibling aged 14 years had an unusually dry skin and complained of the heat and his teeth were widely set and peg-shaped and the upper set numbered 10 originally. Of these 5 had been lost, and the lower teeth totalled 18 only. There were no signs of a second dentition and roentgen examination of the jaws revealed no germ-cells of the permanent teeth. The nails were thin and dystrophic; some were slightly spoon-shaped and others slightly separated in the terminal portion from the nail-bed, and the nail on the left index finger covered only half the nail-bed. There was another male sibling, aged 20 years, and two female siblings aged 3 years who were quite normal — there was no reference to the mother's ancestry.

This family record of BRAIN is given in some detail because it supports the belief of LEVIT (1936) that the dysplasia is always sex-linked but may be incompletely recessive or conditionally dominant in some families so that heterozygous females may have the dysplasia, if in a milder form than it occurs in males. COCKAYNE (1937) affirmed that the trait could be partly dominant in some cases. These explanations apply to most families which show direct descent but if the pedigree published by BATTERSBY (1936) and which COCKAYNE (1937) quoted, be correct, there was direct descent from father to son which was not admitted as being possible if it were sex-linked recessive or dominant, and so COCKAY-

NE considered BRAIN'S family's trait to be autosomal and conditionally dominant.

WEECH (1929) did not put the spontaneous development of a genetic mutation without the bounds of possibility, and did not consider such a possibility as a chance or accidental mutation but as an "expression of a suppressed tendency to change which is inherent in the make-up of the genes themselves." Those cases which might have happened in this spontaneous manner would include those without any antecedent family history and both the sudatory type with more or less of the other characteristics such as my case 2, and the anhydrotic type like MCCRACKEN'S case (1931) in which there was no evidence of hereditary transmission in the two preceding generations nor any collateral evidence in the siblings indicating parental origin.

Case reports

Case 1. A. B. This girl, aged 4 1/2 years, attended the out-patient department of the hospital for the complaint of failure to gain weight, insomnia and anorexia.

Previous history. When she entered her third year she was treated by her doctor for a dry state of her hands which were also red with a thickened skin which had a tendency to crack. Her doctor at one time wondered whether she had pink disease, but the skin of her face and scalp had been dry since babyhood and at times she suffered from heat-spots. She was liable to frequent colds which were accompanied by a thick brownish-red discharge from the nose. Nocturnal enuresis was an additional complaint and she had received medical attention for threadworm infestation. She had suffered no infectious diseases, accidents nor operations.

Her weight had been 3 kg at birth at term. The mother's pregnancy and labour had progressed normally. She began to cut her teeth at the age of nine months but in a noticeably irregular pattern. At 2 1/2 years she weighed 12 kg and at 4 1/2 years only 13 kg. She had never lost weight but the weight gain had been extremely slow. Supplementary vitamin intake had been adequate since 9 months of age.

Physical examination. The weight was well below average for her age of 4 1/2 years. She was quite well nourished but rather frail and of small stature. She was of fair colour and not unusually pale. She was of a remarkable, phlegmatic disposition and cooperated very well at the time of examination. One did not get an impression of mental backwardness.

The head was of normal shape and size. The anterior fontanelle was closed. The hair of the head was dry, fair, fine, short and scanty, especially at the sides of her head where the underlying scalp could be readily seen. It was no more than 15.25 cm in its longest strands and it had never been cut.

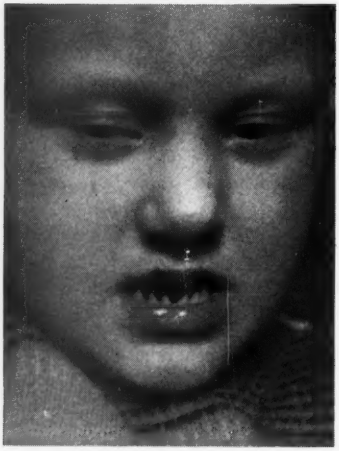

Fig. 1. Showing the typical dental dysplasia in the form of conical teeth of the first dentition. Case 1.

The eyes themselves showed no abnormalities. The orbital regions were striking in that while the supra-orbital ridges were not unduly prominent, the eyebrows were absent and their place taken by very fine and short lanugo-like hair. The upper and lower eyelashes were present and showed no deficiency but there was a wrinkling of the delicate skin of the upper and lower eyelids. The child suffered no lachrymal deficiency. The bridge of the nose was not saddle-shaped, if a little broad, but at the time of examination there was no nasal discharge. The lips were rather full and the lower slightly protuberant. The teeth were remarkable in appearance and the family doctor's descriptive apellation most apt — "shark's teeth." The two upper central incisors had decayed leaving only the carious roots which were septic but the remaining incisors and the canines were remarkably conical and pointed in their configuration and similarity and the two lower central incisors had a vicious lateral slant which gave the dental display a most carnivorous expression. (See Figs. 1 and 2). The remaining teeth of the fully erupted temporary dentition appeared normal. The rest of the buccal cavity was essentially normal. The skin was generally glabrous and dry but there was present over the usual distribution of trunk and extremities a very fine lanugo hair which was very short. Perspiration was not detectable, the skin being very dry. The hands especially were noteworthy. Here the skin was a dusky red over both palmar and dorsal aspects, rather hard with loss of elasticity and a tendency to crack along the natural creases. The

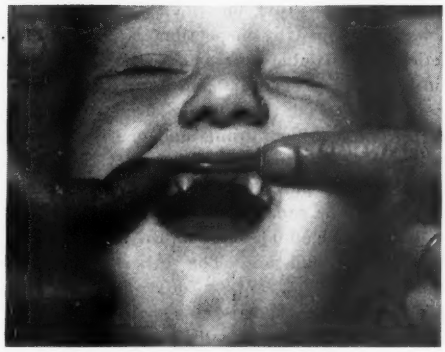

Fig. 2. To show the absent upper central incisors and conical lateral incisors. Case 1.

nails did not extend as far as the tips of the fingers but the nails had never been cut. There were small focal areas of pallor at the tips of the 2nd, 3rd and 4th fingers. This description applied also to the nails of the toes except for the focal points of pallor. The feet, however, while reddier than the skin generally were less red than the hands nor was the skin as dry or thickened or cracked.

The heart. Over the whole precordium was a grade I systolic murmur which was slightly roughened. Its maximal intensity was over the point of maximum impulse inside the nipple line in the fourth intercostal space. No diastolic murmur was audible and the pulses, radial and femoral, were not abnormal on palpation. The rhythm was a regular sinus. Audible over the aortic region, however, was a venous hum.

Special investigations. A roentgenogram of the jaws was taken to check for the presence or absence of tooth-germs of the second dentition. These were not present.

The child was given 3.25 mg of pilo-carpine per os to help evaluate the presence of sweat glands and the responses to this sudorific seemed limited to the palms of the hands, groins, armpits, and the sides of the nose, where a slight dampness only was detectable but no obvious perspiration.

Family history. The foregoing examination led to a detailed questioning of a very cooperative mother for other evidence of ectodermal dysplasia in her family. She was able to give the following information. The mother recalled having two conical upper lateral incisors of her first dentition which were replaced by almost identical incisors of her second dentition. She also recalled having sparse hair on her head until well on into adolescence but no axillary hair until well on into adult life when

her axillary hair began to grow, but not thickly. The sparseness of her axillary hair was confirmed by inspection. However, she affirmed that she had no deficiency of pubic hair which had appeared in late adolescence. Her skin had always been dry and with the exertion and expenditure of energy over her wash-tub she had been aware of perspiration of the skin about the face, axillae, groins and perineum but not elsewhere. She often remarked to herself upon this inability to sweat generally. She was not aware of any comparable condition in her forbears but she had four other children by the same husband: a male aged 18 years, a male aged 13 years, a female aged 11 years and a male aged 2 years, all well without a comparable condition. The other daughter, however, had until 3 years of age, only a central "coxcomb" and was bare at the sides of the head; but since 3 years of age she had grown a good head of hair. Both girls had been practically bald at birth but the boys had been born with good heads of hair which were retained.

The patient's sister perspired normally and the brothers were normal in every way but none of the children had good teeth. All the boy's teeth began to decay at about 18 months of age but their second dentitions erupted normally.

Case 2. J. C. C. This infant was referred to me by Dr. Helen Morley as an interesting case of ectodermal dysplasia which she had come across during her routine attendance at a Babies Welfare Centre. There was no specific complaint. The parents were young, alive and well and not unduly concerned about their child's appearance. No antecedents or collateral relatives were known to have anything similar in the way of ectodermal defects. No evidence was forthcoming of hereditary transmission.

Previous history. She was born at term after a normal gestation and was below average birth weight. She had contracted no illnesses whatsoever and suffered no operations nor accidents. However, at birth this baby had a head of thick dark hair which depilated completely within 2 days. Also the child had no nails at birth but they appeared at 2 weeks of age and grew normally.

Physical examination. A very well nourished, well developed and healthy female child, 10 months of age and of quite pleasing appearance. Birth weight 2.6 kg. Length was 67 cm. Weight was 8 kg. She was of good colour. The feature that was immediately striking was the almost complete absence of hair from the scalp (see fig. 3).

The head was of normal shape and average size with an almost completely closed anterior fontanelle. The eyes were normal and there was slight prominence of the supra-orbital ridges. There was no trace of hair anywhere on the skin except for the few hairs on the scalp. It was possible to count the few eyelashes projecting from the upper eyelids, they were so few, and these were unevenly distributed along the margin

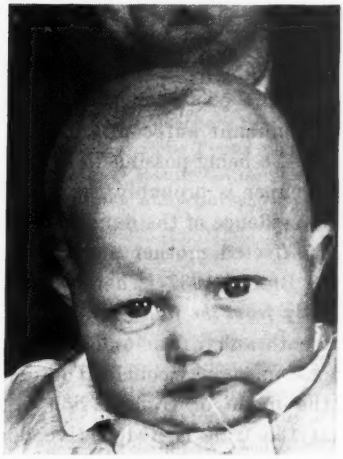

Fig. 3. Case 2. The almost completely bald scalp, absent eyebrows and deficient eyelashes are quite striking.

and of uneven length. There were no eyelashes at all on the lower lids. The bridge of the nose was normal and there was no sign of rhinitis.

The lips were not full nor thick, the buccal cavity was normal and the two lower central incisors had just erupted, rather late, but the erupting teeth were normal in appearance. Although no hairs were present on the smooth glabrous skin except as already indicated, the child had sweat glands and occasional spells of vigorous crying provoked perspiration generally. The nails of toes and fingers did not deviate from the normal. X-rays of the jaws did not show a deficiency of tooth germ-cells. The rest of the systemic physical examination was normal.

Comment

The foregoing brief review and 2 personal case reports of ectodermal dysplasia are submitted to show that these strange ectodermal dysplasias even in the fully developed state do not necessarily follow a fixed pattern. The large majority of cases have been males although in 1848 when THURNAM reported the 2 male cousins who were of the anhydrotic type, WILLIAMS was able to report the first case of this type in the female. It was only after a long interval that a second female case of ectodermal

dysplasia was published and this case, GOECKERMANN'S, was also anhydrotic. Various authors have brought strong evidence to show that the anhydrotic type is a sex-linked recessive appearing in males only and, while postulating that ectodermal dysplasia in the female is a dominant autosomal, have not accounted for the anhydrotic type also being possible in the female. It is believed that case 1 of this paper is probably the first to be reported in which there is good evidence of the daughter inheriting the defect directly from her affected mother and that it is analogous to the case report of BRAIN (1937) where the defect in the sons was inherited directly *from the father* who had the trait to a very mild degree. That both anhydrotic and sudatory types are transmissible in each sex seems pretty conclusive from the case histories. To account for the mode of transmission in my case 1, I can but postulate that the trait is a defective dominant linked to one X-chromosome of the mother and that this linkage could give rise to half the sons and half the daughters becoming affected.

Summary

Two case reports of ectodermal dysplasia in two females are presented. One case is believed to be the first reported with evidence of direct descent from mother to daughter. The other is a case of the mendelian dominant type. The submission is made that the anhydrotic type is not necessarily always a sex-linked recessive manifestation in males but that both types, anhydrotic sex-linked recessive, and dominant, may occur in each sex although more frequently in the male.

I wish to thank Mr G. Ward, the photographer to the hospital, for the photographs.

Dysplasie ectodermique.

On rapporte deux cas de dysplasie ectodermique chez deux jeunes filles. On suppose que l'un des cas est le premier rapporté avec la preuve de descendance directe de mère à fille. L'autre est un cas de type mendélien dominant. L'hypothèse suivante est soumise: le type anhydrotique n'est pas nécessairement toujours la manifestation d'un caractère genetique récessif chez les hommes, mais les deux types facteur genetique recessif anhydrotique, et dominant, peuvent se rencontrer dans chaque sexe, quoique plus souvent chez l'homme.

Ektodermale Dysplasie.

Es wird über zwei Fälle von ektodermaler Dysplasie weiblichen Geschlechts berichtet. Der eine Fall mit nachgewiesener direkter Vererbung von Mutter auf Tochter soll erstmalig beschrieben worden sein. Der andere ist ein Fall von Mendel'schem dominanten Typus. Es wird hervorgehoben, dass der anhydrotische Typus nicht immer eine unbedingt geschlechtsgebundene rezessive Manifestation bei Männern ist, sondern dass beide Typen, sowohl der anhydrotische rezessive, als auch der dominante bei beiden Geschlechten, häufiger jedoch beim männlichen Geschlecht, vorkommen können.

Displasia ectodermica.

Se describen 2 casos de displasia ectodermica en 2 sujetos del sexo femenino. En uno de los casos se considera ser el primero descrito con evidencia de descendencia directa de madre a hija. El otro es un caso de herencia mendeliana. Se llama la atención que el tipo anhidrótico no es necesariamente siempre una forma de manifestación recesiva ligada el varón, sino que ambos tipos tanto el anhidrótico recesivo ligado al sexo como el dominante pueden ocurrir en cada sexo aunque mas frecuentemente en el varón.

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FROM THE CHILDREN'S CLINIC, UNIVERSITY OF HELSINKI. CHIEF: PROFESSOR ARVO YLPPÖ.

Effect of Potassium Therapy in Severe Infantile Gastroenteritis

by

NIILO HALLMAN

In recent years, solutions containing potassium have come into use in the treatment of dehydration, to replace the potassium lost by the organism in that state. Since the publications of GOWAN and DARROW and DARROW (1946) of their results obtained by this method of treatment of infantile gastroenteritis, no reports comparing the results of treatment with and without potassium have, to my knowledge, appeared in the literature. I therefore considered it advisable to publish a study of 70 cases of extremely severe infantile gastroenteritis treated in 1949 in the Children's Clinic of the University of Helsinki, half of them were treated by the older methods without administering potassium, and the other half were given potassium mainly on the lines suggested by DARROW.

Since 1940 there has been a high incidence of severe gastroenteritis among infants in Finland. In evidence we have the vital statistics of the whole country; deaths resulting from infantile gastroenteritis between 1941 to 1949 inclusive were 0.51—1.18 per cent yearly, calculated from the total infant mortality of 4.94—6.84 per cent (LOUHIVUORI and NEVANLINNA) for the same period. Serious cases are brought to the Cildren's Clinic of the University from all over the country, and the journey can sometimes last several days. It is easy to understand that the condition of the patients is often extremely poor. So far investigations have not brought to light the causative agent of gastroenteritis and this has also been the case in this series. Epidemics among the new-

born, such as have been described in other countries, have not been found in Finland. None of the patients in this series was transferred for treatment direct from a maternity hospital.

Material

The first 35 patients of this series, treated without potassium, were admitted between March and July, 1949. The other 35 treated with potassium were admitted between August and December of that year. It has been our experience previously that cases are most severe in late summer or autumn, and therefore the time of onset cannot have had a favourable effect on the group treated with potassium.

The patients were included in this series without any selection whatever; i.e., all the cases classified as serious immediately on admission. The qualifications were: manifestation of toxic symptoms, clearly disturbed consciousness, with the exception of some cases of deep unconsciousness, and severe dehydration. The weight prior to the onset of gastroenteritis could not be checked, and therefore the assessment of dehydration was made on the basis of the clinical picture. The weight of all these patients was unmistakably below that of normal infants of the same age.

Therapeutic Methods

Patients treated without potassium:

Immediately on admission, and in order to counteract the shock, the patients were given plasma (20 ml per kg body weight), as a slow infusion into the superficial veins of the head. Simultaneously, stimulants were administered. Before this blood specimens were taken for determining the plasma proteins, alkali reserve and chloride. If the patient was in a particularly poor condition, and especially if respiration indicated acidosis, 1.3 per cent sodium bicarbonate (10 ml per kg of body weight) was introduced directly into the vein, also as a slow infusion, even before the results of the chemical analysis became known.

If the alkali reserve of the specimen examined was below 15 mEq/l, the same amount of bicarbonate was infused a second time. It was given approximately 2 hours after the administration of the first infusion. Later it was only necessary to give the bicarbonate solution on the

following days in exceptional cases, and only if the alkali reserve persisted below 15 mEq/l.

Fluid therapy, when vomiting was absent, was afterwards continued per os or, if vomiting was abundant, as in all our cases, the subcutaneous method of Hartmann was used. The following solution (100—150 ml per kg body weight) was given daily: 1/3 physiological NaCl solution, 1/6 1.87 per cent sodium lactate and 1/2 5 per cent glucose. In addition, 10 per cent glucose was given by mouth or subcutaneously, so that the total fluid amount varied, according to the weight, between 150 and 200 ml per kg body weight daily. Calcium was also administered, when need arose. As soon as the alkali reserve returned to normal, one proceeded to give a solution containing 4/5 5 per cent glucose and 1/5 physiological NaCl solution. If the plasma protein level was low, additional plasma was given intravenously. Parenteral administration of fluid was immediately discontinued as soon as it was possible to give this by mouth.

Patients treated with potassium:

The treatment followed the lines suggested by *Darrow*, with the exception of the administration of alkali therapy. The initial proceedings were the same as in the other group. Depending on the alkali reserve results obtained, 1.3 per cent bicarbonate was given as follows:

Alkali reserve below 9 mEq/l	—	15 ml.	per	kg	body	weight
9—11	»	»	»	»	»	»
11—14	»	»	»	»	»	»

Immediately after this Darrow's solution (NaCl 3.0, KCl 2.7 $NaHCO_3$ 4.4, Aq. dest. ad 1000.0) was instituted subcutaneously; the usual amount was 60—80 ml daily. As soon as the alkali reserve had returned to normal, the bicarbonate of the solution was replaced by glucose (NaCl 2.9, KCl 3.7, Glucose 20.0, Aq. dest. ad 1000.0). Simultaneously with the increase of fluid administration per os, parenteral therapy was reduced. The total fluid amount, of which the balance was given as glucose solution, was as equally large as that of the other group. Plasma was administered when need arose.

Diet

Both groups were on a diet of breast milk, and it was usually started after 1 to 3 days fasting, depending upon the character of the stools and their frequency, as well as on vomiting. The salt solutions were gradually reduced and their administration discontinued if the alkali reserve remained normal, and if breast milk could be given per os in sufficient amounts (i.e. 400 ml daily).

Chemotherapy was not instituted, except in the treatment of complications.

Table 1.

Age at onset of disease Months	Treated without K		Treated with K	
	Recoveries	Deaths	Recoveries	Deaths
≦ 1	1	2	6	0
> 1 ≦ 3	12	7	11	5[1]
> 3 ≦ 6	6	5	7	2[2,3]
> 6 ≦ 9	1	1[4]	4	0
	20	15	28	7

[1] Thrombosis of the superior sagittal sinus.
[2] Purulent meningitis.
[3] Chronic pneumonia of the right upper lobe.
[4] Bronchopneumonia of the left upper lobe.

Results

Among the 35 patients belonging to the first group, i.e., those treated without potassium, 15 babies or 43 per cent died. Among the other group treated with potassium 7 or 20 per cent died.

Autopsy was performed on all those who died, and the results were these commonly in gastroenteritis. However, bronchopneumonia was discovered in one patient in the first group, and it was obvious that it was at least partly responsible for the fatal outcome. Among the patients in the second group there was one who had also bronchopneumonia. In addition, one of the patients, having more or less recovered from gastroenteritis, fell ill with purulent meningitis (Salmonella enteritidis), and this latter must be considered as the ultimate cause of death. Moreover, one patient revealed thrombosis of the sagittal sinus, evidently as a consequence of the gastroenteritis. All these four cases had already recovered to a great extent from the diarrhoea at the time of death, and it was obvious that fluid therapy was powerless to affect the course of the disease. If we exclude these 4 cases, on whom fluid therapy could evidently have no influence, *the mortality rate among those treated without potassium is 41 per cent, and with potassium 13 per cent.*

The age of the patient is known to affect the prognosis of

Table 2.

Duration of disease before admission to hospital Days	Treated without K		Treated with K	
	Recoveries	Deaths	Recoveries	Deaths
≦ 1	2	1	3	0
> 1 ≦ 3	3	5	7	2 [1, 3]
> 3 ≦ 10	10	5 [4]	15	3
> 10	5	4	3	2 [2]

[1, 2, 3, 4] as in Table 1.

infantile gastroenteritis in so far as the outlook is the poorer, the younger the baby. In *Table 1* the patients are grouped according to the age at onset. We note that there were 22 babies under 3 months of age in each group, i.e., exactly the same number. There were more infants under one month in the group treated with potassium than in the other. Both babies over 3 months old who were treated with potassium and died, revealed at autopsy the complications already referred to. It is therefore obvious that the better results yielded by the potassium therapy in this series cannot at any rate be ascribed to the age grouping of the patients.

Ill-health of long duration aggravating the general condition can affect in part the prognosis in toxicosis following the disease. So-called cholera infantum is known to lead to death within some days or even hours. In *Table 2* the patients are classified according to the duration of the disease before admission. In both groups there was an equal number of infants with an acute onset and severe symptoms, i.e., 12. Among those treated without potassium there were 6 deaths compared with 2 in the other group. The latter two developed complications. In the former group there were 9 babies who had been ill for more than ten days before the acute stage set in, with a corresponding figure of 5 in the latter group. There were 4 and 2 deaths respectively, and one of these latter two contracted meningitis afterwards. It is also obvious that the classification of the material on this basis cannot have affected the prognosis in the two therapy groups.

Table 3.

Duration of disease in hospital before death or beginning of gain in weight Days	Treated without K		Treated with K	
	Recoveries	Deaths	Recoveries	Deaths
≦ 1	0	2	0	1
> 1 ≦ 3	0	3	0	1
> 3 ≦ 10	0	6[4]	2	1
> 10 ≦ 20	4	3	15	0
> 20 ≦ 30	6	1	8	0
> 30	10	0	3	4[1, 2, 3]

[1, 2, 3, 4] as in Table 1.

Table 3 shows the material grouped according to the duration of treatment, taking into account, in regard to the recoveries, the time of residence in hospital, after which the weight had begun to show a steady gain. Among those treated without potassium there were two deaths in the course of the first twenty four hours, and one death in the group treated with potassium. It would appear that these cases could not in any way be affected by fluid therapy. During the first ten days of treatment 11 babies succumbed in the first group and 3 in the latter. Of those on potassium therapy one died after one month of treatment, but three of them had some complication as already mentioned. It is obvious that the most clear-cut difference in the prognosis of those treated with or without potassium can be seen during the first few days of treatment.

If we study the period during which the weight has begun to rise again (Table 3) we find that the gain started within the first 20 days for 17 infants of the 28 who recovered on potassium therapy. For the parallel group, only 4 of 20 recoveries had begun to gain in weight during the same period. One half of the patients belonging to this group only began to increase in weight after one month of treatment. It seems evident that potassium plays a part in promoting a quicker recovery during the initial stage of the disease.

The level of the alkali reserve at the time of admission has

Table 4.

Plasma bicarbonate on admission to hospital mEq/l	Treated without K		Treated with K	
	Recoveries	Deaths	Recoveries	Deaths
≦ 10	4	3	10	1 [1]
> 10 ≦ 15	11	7 [4]	16	1 [2]
> 15 ≦ 20	4	3	3	2
> 20 ≦ 25	1	2	0	2 [3]

[1, 2, 3, 4] as in Table 1.

been used as a standard for assessing the severity of the disease (FLETT, PRATT and DARROW). Another grouping of the material on this basis is shown in *Table 4.* It shows that this level was below 15 mEq/l in 25 infants treated with potassium and in 28 treated without it. In this respect the series are comparable to each other. However, it must be taken into account that the death rate was proportionately higher in those groups in which the alkali reserve was not reduced. The effect of potassium therapy is most pronounced in those cases which were strongly acidotic on admission to hospital. In the group of patients treated with potassium there were two deaths among the 28 infants who were strongly acidotic at the time the treatment was instituted, and these deaths were also largely due to the complications already referred to. In comparison, of the 25 treated without potassium 10 died; one, however, died as a result of bronchopneumonia at a later stage of the disease.

Moreover, it must be mentioned that the plasma potassium concentration was below 2 mEq/l when death occurred in two cases belonging to the group without potassium. All in all, the potassium level fell below 3 mEq/l in 14 cases of this group, at some stage of the disease. However, no account of this whatever was taken while treatment was in progress, since, owing to lack of laboratory facilities, the potassium determinations had to be carried out after the patients had been discharged, i.e., the specimens were taken during the course of the disease and stored. Among those treated with potassium the plasma potassium was

below 3 mEq/l in 5 cases. As the results of the blood chemistry investigations will be published in a separate article, it is not necessary to discuss this aspect in more detail here.

Comment

Balance tests performed by previous investigators have demonstrated that the infant organism affected with gastroenteritis retains potassium in the convalescent stage (DARROW, FLETT, PRATT, GAMBLE and WIESE; BUTLER, TALBOT, CRAWFORD, MACLACHLAN and APPLETON), and the administration of potassium to these patients is based on this finding. Furthermore we know that the organism maintained on a diet poor in potassium, loses it if sodium chloride is administered (WILEY, WILEY and WALLER). The amounts of glycogen which must be stored by a gastroenteritis patient who receives glucose, serve to bind the potassium (FENN). Cases have also been reported who, in the stage of convalescence from gastroenteritis, presented symptoms of heart function disorders, simultaneously with a fall in plasma potassium. (GAMBLE, WIESE and HANSEN; WALLACE and MOLL.)

In this series the mortality rate among those treated with potassium is lower than for those treated without it. The result therefore lends support to the conclusions drawn by previous investigators as to the value of the use of potassium in treating infantile gastroenteritis. In both those cases which were treated with solutions free from potassium the plasma potassium was found to be below 2 mEq/l. Both cases ended fatally. The heart function, either of these two or of the other patients in this series, was not studied. Autopsy did not reveal anything abnormal in the heart. Yet the plasma potassium concentration must have played its part in the fatal issue. Especially in those cases of pronounced acidosis who, when treated without potassium, succumbed within the next few days, in the course of which the potassium deficiency, theoretically speaking, is highest, mortality was practically non-existent in this series.

Among the recoveries, those patients who had been treated with potassium showed a more rapid recovery in the initial stages

than those treated without it. It is probable that the supply of potassium in that stage when it is needed by the organism, i.e., when the extracellular fluid returns to normal and the cell function revives, helps the whole organism to a more rapid recovery.

Summary

A study is made of 70 cases of severe infantile gastroenteritis; half of the patients were treated by subcutaneous administration of solutions containing potassium during the first few days of treatment, and the rest were given solutions free from potassium for a corresponding length of time. Therapy was similar in all other respects.

Both groups are similar in regard to age, picture of the disease, duration prior to admission and alkali reserve at the begining of treatment.

Of the 35 infants treated without potassium 15 died, compared with 7 in group treated with potassium. One of the former group had bronchopneumonia discovered at autopsy. In the latter group one also had bronchopneumonia, one purulent meningitis, and another thrombosis of the sagittal sinus. If these cases, whose prognosis was obviously unaffected by the fluid therapy are excluded, the mortality rate of those treated without potassium was 41 per cent and for those treated with potassium 13 per cent. The recoveries belonging to the latter group showed on an average a more rapid gain in weight than patients treated without potassium.

The advantage of potassium therapy is evidenced by the result.

Effet du traitement par le potassium dans des cas de sévères gastro-entérites infantiles.

Une étude est faite de 70 cas de sévères gastro-entérites infantiles: la moitié des malades a été traitée par l'administration sous-cutanée de solutions contenant du potassium pendant les quelques premiers jours de traitement, et l'autre moitié a reçu des solutions dépourvues de potassium, durant la même période. Le traitement était, par ailleurs, tout à fait identique. Un parallélisme peut être établi entre les deux groupes en ce qui concerne l'âge, le tableau de la maladie, le temps écoulé avant l'admission et la réserve alcaline au début du traitement. De ces 35 enfants traités sans potassium, 15 sont morts, le chiffre étant de 7 dans le groupe équivalent traité avec du potassium. Un des malades du premier groupe a eu une bronchopneumonie confirmée à l'autopsie. Dans le deuxième groupe, l'un a eu aussi une broncho-pneumonie, l'un une

méningite purulente, et un autre une thrombose du sinus longitudinal. Si on exclut ces cas dont le pronostic a été, de facon évidente, inchangé par la thérapeutique hydrique, le chiffre de mortalité des malades traités sans potassium est de 41 %, et parmi ceux qui ont été traités avec potassium de 13 %. La convalescence des malades du deuxième groupe montre, en moyenne, un gain de poids plus rapide que parmi ceux qui n'ont pas recu de potassium. Les avantages du traitement par le potassium sont évidents d'après ces résultats.

Erfolg der Kalium-Therapie bei schwerer Gastroenteritis.

Studie über 70 Fälle schwerer kindlicher Gastroenteritis. Die Hälfte der Patienten wurde in den ersten 5 Tagen mit subcutan verabfolgten Lösungen behandelt, welche Kalium enthielten; die andere Hälfte der Patienten bekam entsprechend lange kaliumfreie Lösungen. Sonst in beiden Versuchsreihen ähnliche therapeutische Massnahmen. Beide Gruppen waren ähnlich in Bezug auf Alter, Krankheitsbild, Krankheitsdauer bis zur Aufnahme und Alkalireserve bei Behandlungsbeginn. Von 35 Kindern, welche ohne Kalium behandelt wurden, starben 15, dagegen nur 7 in der mit Kalium behandelten Gruppe. In der ersten Gruppe wurde in einem Fall eine Bronchopneumonie bei der Autopsie entdeckt, in der zweiten Gruppe auch ein Fall von Bronchopneumonie und je ein Fall von Meningitis purulenta und Thrombose des Sinus sagittalis. Wenn diese Fälle, deren Prognose durch die Flüssigkeitstherapie offensichtlich nicht beeinflusst wurde, nicht berücksichtigt werden, beträgt die Mortalität ohne Kaliumbehandlung 41 %, mit Kalium 13 %. In der Rekonvaleszenz zeigt die letztere Gruppe raschere Gewichtszunahme als jene ohne Kaliumbehandlung. Die Vorteile der Kaliumtherapie werden durch diese Resultate unterstrichen.

Efecto de la terapéutica con potasio en las formas severas de gastroenteritis infantil.

Se hace un estudio de 70 casos de gastroenteritis infantil severa; la mitad de los pacientes fueron tratados por la administración subcutánea de soluciones conteniendo potasio en los primeros días de tratamiento y la otra mitad recibieron durante el mismo período soluciones que no contenian potasio, en ambos grupos se siguió en los demás aspectos una terapéutica similar. Puede establecerse un paralelismo en ambos grupos en lo que se refiere la edad, cuadro clínico duración previa de la enfermedad y reserva alcalina al comienzo del tratamiento. De los 35 niños tratados sin soluciones potásicas 15 murieron, mientras que del grupo que recibió la terapéutica con potasio solo fallecieron 7. Uno de los niños del primer grupo tenía una bronconeumonia que se comprobó en la

autopsia. Y entre los del segundo grupo, uno presentaba una bronconeumonia, otro una meningitis purulenta y en otro una trombosis del seno sagital. Si estos casos cuyo pronóstico no podía ser afectado por la terapéutica con infusiones son excluidos, la cifra de mortalidad que se obtiene para el grupo tratado sin soluciones potásicas es de 41 % y en el grupo tratado con las soluciones de potasio de solo 13 %. La recuperación de los niños de este segundo grupo mostraba un promedio de mayor rapidez también en lo que se refiere al aumento de peso que en los pacientes tratados sin potasio. Las ventajas de esta terapéutica por el potasio quedan bien evidentes con estos resultados.

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FROM THE CHILDREN'S CLINIC (CHIEF: PROFESSOR T. SALMI, M. D.) AND THE SERO-BACTERIOLOGICAL INSTITUTE (CHIEF: PROFESSOR E. MUSTAKALLIO, M. D.) UNIVERSITY OF TURKU, FINLAND

On the Activity of Chloramphenicol against Haemophilus Influenzae with Special Reference to Influenzal Meningitis

by

J. A. GRÖNROOS

Since the beginning of 1948 sensitivity tests have been carried out at the Sero-Bacteriological Institute on 28 different strains of Haemophilus influenzae using various drugs. The source and type of these strains can be seen in Table I.

Methods: Specimens of cerebrospinal fluid from cases diagnosed as meningitis are cultured on blood agar, into liver broth, thioglycolate-containing broth, and on McLeod culture medium on two plates, of which one is incubated in air of 5—10 % CO_2 content. If on the basis of gram-stain there is reason to suspect a Haemophilus infection, then staphylococcal colonies are cultured on blood agar in order to make the satellite phenomenon appear. Haemophilus influenzae grows richly on McLeod's culture medium in a CO_2 atmosphere, but only as satellite foci round the staphylococcal colonies on blood agar. Like some other pathogenic bacteria the Haemophilus influenzae strains have often required an incubation of 48 hours. Negative results have not, therefore, been reported until after two days incubation.

The serological typing has been performed from a culture of Haemophilus influenzae grown in Levinthal broth for 6 hours, or straight from cerebrospinal fluid with rabbit immune serum on the basis of the swelling reaction of the capsule (ALEXANDER 1948).

The sensitivity tests have been carried out by the plate method: Into the plates the Levinthal or Fildes agar and drugs were added in various dilutions. On those was cultured a loopful of 18 hours'-incubated Levinthal broth diluted to 1: 200. According to ENGBAEK (1949) a culture incubated for 18 hours rather constantly contains approximately 3000 million bacteria in a ml. The reading of the results was performed by noting the minimal concentration producing total inhibition.

Table I.

Sources and types of the strains.

Source	Nos. of strains	Nos. of type B
Spinal fluid	14	6 of type B (8 untyped)
Middle ear	1	Type B
Eye	5[1]	4 of type B (1 unknown)
Empyema pleurae	1	(untyped)
Abscessus reg. coxae	1	(untyped)
Abscessus fossa Douglasi	1	Type B
Sputum	6	4 of type B (2 unknown)

The estimation of the chloramphenicol content of spinal fluid and serum has been made by titrating them in twofold dilutions and then testing their bacteria-checking influence on the growth of Haemophilus infuenzae strains in half-liquid Fildes agar culture medium. In connection with these tests the sensitivity of the strain in question has been tested at the same time and according to the results the chloramphenicol content corresponding to the greatest inhibiting dilutions of the abovementioned fluids has been calculated. The readings have been performed after a growth of 24 hours.

The drug sensitivity of the strains tested can be seen in Table II. The strains have generally been sensitive to all antibiotics, but resistant to sulphathiazole and sulphadiazine. TUNEVALL (1951) has recently published the drug-sensitivities of 63 Haemophilus influenzae strains to various antibiotics, describing at length the earlier literature. The sensitivities of the strains reported in this paper are of the same order as those of TUNEVALL but somewhat more sensitive to penicillin than usual. LAHIKAINEN (1951) has reported that the chloramphenicol sensitivity of the Haemophilus influenzae strains he has taken from cases of otitis media varies from 0.08 to 0.6 microg/ml. The average chloramphenicol sensitivity of the 22 strains in the present series was 0.86 microg/ml, the sensitivity varying from 0.1 to 5 microg/ml. Thus the Haemophilus influenzae strains found at Turku have been sensitive to chloramphenicol.

[1] Isolated by Dr. K. JÄNTTI, Assistant at Eye Clinic of the University of Turku.

Table II.

The sensitivity of the Haemophilus influenzae strains isolated at the Sero-bacteriological Laboratory in Turku since 1948.

The active compound.	The inhibition concentrations, for Sulphatiazol and Sulphadiazine mg % for others microg									Nos. of strains
	>20	20	10	5	3	2	1	0.5	0.25	
Chloramphenicol ..				1			12	7	2	22
Terramycin				1		1	5	8	1	16
Aureomycin				1		2	7	6	2	18
Streptomycin		2	1	7	7	8	1			26
Penicillin[1].....						1	4	15		20
Sulphatiazol	12	5			1				1	19
Sulphadiazine.....	14						1			15

[1] 1 unit = 0.6 microg.

At the Children's Clinic and at the Epidemic Hospital the prognosis of Influenzal Meningitis (below abbreviated IM) cases treated with streptomycin and sulpha-drugs has been poor, therefore, knowing the sensitivity of the Haemophilus to chloramphenicol, treatment with this was begun. It had already been proved that chloramphenicol passes into the cerebrospinal fluid (Ross et al., Smadel et al. 1949, Grönroos 1950) to about 30—50 % of the serum content. Before the first IM case was admitted to our department Green et al. (1950) had already published one, Carabelle et al. (1950) 5, and Prather et al (1950) 15 IM cases treated with good results with chloramphenicol. McCrumb et al. (1951) have published a series comprising 12 cases with similar good results and Bergström (1951) says that the good results of three IM cases treated with both streptomycin and chloramphenicol were due solely to the latter antibiotic.

Since 1948, 155 acute meningitis cases have been treated in the Children's Clinic and the Epidemic Hospital. Of these 52 were nonbacterial many due to the parotitis virus. The IM ranks second to tuberculous meningitis, with the exception of the latter, the IM: s are about one third of all the bacterial ones.

Table III. Cases of Influenzal Menin-

No.	No. of Journal	Sex	Age in months	Weight in kg	Degree of illnes	Probable day of disease before bacteriological diagnosis	Tera. Treatment before bacteriological diagnosis
1	1265/48	M	11	9	S	4	—
2	87/49	M	4	4.9	S	?	P 25 000 u i. th. P 25 000 u i. m.
3	318/49	F	14 1/2	8.75	L	7	P 45 000 u i. th. P 280 000 u i. m.
4	525/49	M	38 1/2	13	S	2	P 10 000 u i. th. P 160 000 u i. m.
5	746/49	F	7	7.3	S	12	P 80 000 u i. th. P 540 000 u i. m.
6	1119/49	F	7	6.2	M	4	P 160 000 u i. m.
7	1374/49	F	8	9	S	5	—
8	1064/50	F	23	13.5	L	6	P 630 000 u i. m. Str 0.48 g i. m.
9	84/51	M	12	9.5	S	5	P 150 000 u i. m. Sd 2 g p. o.
10	491/51	M	14 1/2	12	S	4	P 50 000 u i. th. P 400 000 u i. m.
11	1011/51	M	3	4.6	S	3	Sd 1.5 g p. o.
12	723/51	F	11	7.9	L	8	P 240 000 u i. m. Sdm 3 g p. o.
13	—	M	47	14 1/2	S	5	P 20 000 u i. th. P 100 000 u i. m.

Key: S = severe, M = medium, L = slight
P = penicillin, Str = streptomycin, C = chloramphenicol
Szl = sulphathiazole, Sd = sulphadiazine, Sdm = sulphadimedin

gitis Treated in Turku since 1948.

peutics			Spinal fluid		
Dosage and administration/kg body weight/day and the total after bacteriological diagnosis			Sterile on *n*:th day after beginning of the specific treatment	Cell counts normal in *n* days	Results of treatment
P	1 555 u	45 000 u i. th.	8th	24	Recovered
P	17 780 u	800 000 u i. m.			
Str	2 mg	190 mg i. th.			
Str	18 mg	1.8 g i. m.			
Szl	0.33 g	72 g p. o.			
Str	10 mg	0.4 g i. th.	—	—	Died
Str	60 mg	3.1 g i. m.			
P	1 580 u	60 000 u i. th.	Sterile before the specific treatment	63	Recovered
Str	2.2 mg	0.023 g i. th.			
Str	74.3 mg	8.32 g i. m.			
P	1 540 u	20 000 u i. th.	3rd	260	Recovered
P	12 300 u	1 440 000 u i. m.			
Str	0.75 mg	0.12 g i. th.			
Str	46.2 mg	16.2 g i. m.			
Str	5 mg	0.5 g i. th.	—	—	Died
Str	111 mg	12.9 g i. m.			
Str	3 mg	0.2 g i. th.	3rd	44	Recovered with sequelae (hydrocephalus).
Str	45 mg	11.7 g i. m.			
Str	3 mg	0.31 mg i. th.	—	—	Died
Str	44 mg	0.4 g i m.			
C	100 mg	10.125 g p. o.	Next day	15	Recovered
C	147 mg	9.7 g p. o.	3rd	[1]	Recovered
Str	1.4 mg	0.165 g i. th.	3rd	37	Recovered
Str	43 mg	8 g i. m.			
C	70 mg	11.75 g p. o.			
C	87 mg	33 g p. o.	3rd	15	Recovered
C	85 mg	4.725 g p. o.	Next day	18	Recovered
C	132 mg	17.7 g p. o.	3rd		Recovered

i. m. = intramuscular
i. th. = intrathecal
p. o. = per os

[1] 26 leucocytes/cmm after 15 days.

In Table III are shown protocols of cases treated. The ages of the patients varied from 3 to 47 months, the average being 15.4. In all cases Haemophilus influenzae was cultured from the spinal fluid, and in cases 8, 10, 11, 12, and 13 the strain could be typed as B-type. Comparison of the degree of severity is difficult, because the glucose values of the spinal fluids could not be estimated. On the basis of their general state they have been classified as severe, medium, or slight.

In the table it will be noticed that the cases treated with sulpha-drugs, penicillin, and streptomycin reacted poorly to the treatment. In the recovered cases the return to normal of the spinal fluid has taken a long time. This may partly depend on the fact that the intrathecal dosage of streptomycin was continued for an average of 12 days. According to ALEXANDER and LEIDY (1947) a five days' treatment would be sufficient. Thus continued intrathecal streptomycin might actually retard recovery (WILSON et al. 1949). In case No. 10, treated with chloramphenicol and intrathecal streptomycin the pleocytosis in the spinal fluid lasted longest. Probably the prognosis would have been better in all the cases treated with streptomycin if a combined haemophilus-immune sérum therapy had been used.

In the IM cases treated with chloramphenicol the pleocytosis in the cerebrospinal fluid has disappeared more rapidly than in the group treated with streptomycin.

The prognosis can be seen in the table, but case No. 13, which was an extremely severe one, deserves some comment.

On admission the patient was unconscious. During the first day it was impossible to obtain any cell count because the cerebrospinal fluid was so purulent that it coagulated immediately. It did not come out in drops, but had to be aspirated. Therefore streptokinase was used, made by P. HEDLUND at the State Bacteriological laboratory in Stockholm. It probably partly caused the remarkably quick decrease in the number of the cells. During the disease a strabismus developed due to a paralysis of the abducens nerves. This has persisted. Otherwise the prognosis of the case resembled the earlier ones.

Charts 1 and 2 show the chloramphenicol content of the spinal fluids of 2 cases. In 5 cases the spinal fluid chloramphenicol

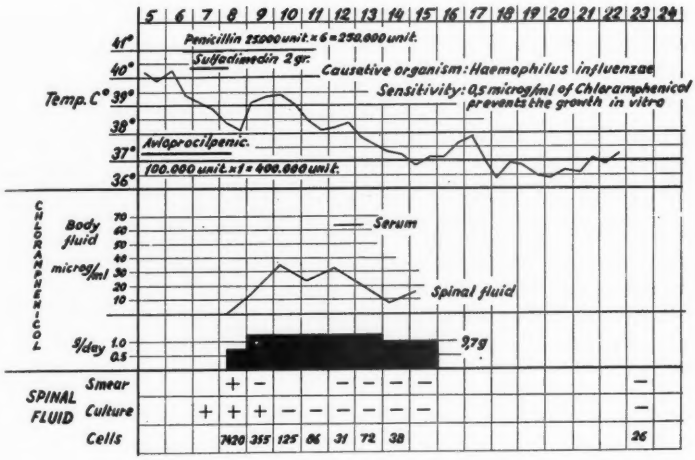

Chart 1. Case No. 10. K. K. ♂ 12 months; weight 9 500 g. D. Meningitis purulenta + Bronchopneumonia.

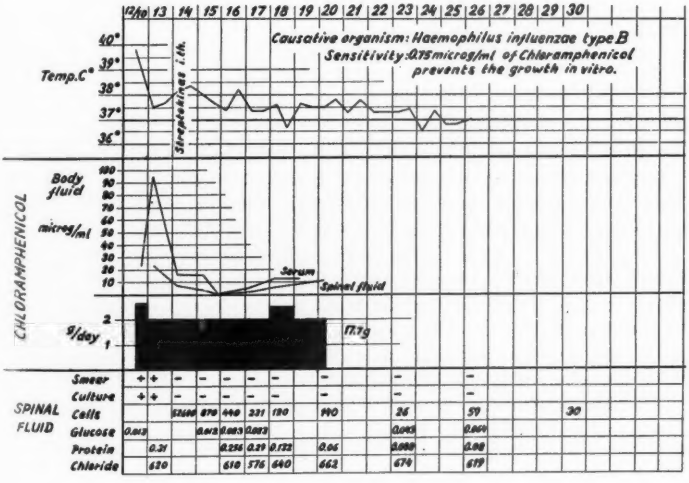

Chart 2. Case No. 13. J. A. ♂ 47 months; weight 14 500 g. D. Meningitis purulenta.

content was found to be from 20—60 times higher than *the sensitivity of the Haemophilus strain cultured in the case in question and used in the very test.* The sensitivity of all the strains cultured from the cerebrospinal fluid has been less than 1 microg. chloramphenicol/ml. In all cases the treatment used before chloramphenicol was begun was unable to inhibit the growth of the Haemophilus strain. On an average a daily dose of 100 mg chloramphenicol per kilogramme of body weight orally has been sufficient to check the infection. Treatment lasted for a week. Obviously the cases have reacted well to the chloramphenicol therapy.

Taking into account the toxicity of streptomycin and the much lower concentration obtained in the spinal fluid with penicillin (FLORY et al. 1949), aureomycin (DOWLING et al., BRAINERD et al., 1949), and terramycin (LINSELL et al. 1950) compared with chloramphenicol, it is clear that chloramphenicol is suitable for the treatment of IM, especially if the case is controlled with bacteriological cultures and sensitivity tests.

Further investigations on a greater number of cases will prove the real value of chloramphenicol in the treatment of IM.

Summary

1. The 22 Haemophilus influenzae strains that were tested were all sensitive to chloramphenicol.

2. With an oral dosage of about 100 mg chloramphenicol per kg per day about 20—60 times greater chloramphenicol content in the spinal fluid was obtained than the sensitivity of the strains cultured from Haemophilus influenzae meningitis cases.

3. Thirteen cases of Haemophilus influenzae meningitis, the average age of which was 15.4 months, the youngest child being 3 and the oldest one 47 months, have been treated as follows: 5 only with chloramphenicol: all recovered; 1 with chloramphenicol and streptomycin: recovered; 7 with streptomycin, penicillin, and sulpha drugs: of these 3 recovered, 3 died, and one recovered with sequelae.

4. The patients treated with chloramphenicol generally recovered more quickly than those treated with streptomycin and other drugs.

Activité de la chloromycétine sur l'Hémophilus Influenzae, particulièrement dans la méningite de Pfeiffer.

1. Toutes les 22 souches de Hémophilus Influenzae qui ont été testées, ont été sensibles à la chloromycétine.

2. Avec une dose d'environ 100 mg par kilo et par jour de chloromycétine, administrée per os, on obtient une concentration de chloromycétine dans le liquide céphalorachidien environ 20 à 60 fois supérieure à la sensibilité des cultures de souches d'Hémophilus Influenzae, retrouvées dans les cas de méningite.

3. 13 cas de méningite à Pfeiffer, dont l'age moyen était de 15,4 mois, le plus jeune enfant ayant 3 mois et le plus agé 47 mois, ont été traités comme suit: 5 avec chloromycétine seule: tous guéris. 1 avec chloromycétine et streptomycine: guéri. 7 avec streptomycine, pénicilline et sulfamides: parmi ceux-ci, 3 guéris, 3 décédés et un guéri avec séquelles.

4. Les malades traités avec chloromycétine guérissent en général plus rapidement que ceux traités avec streptomycine et autres drogues.

Über die Wirkung von Chloramphenicol gegen Haemophilus Influenzae mit besonderer Rücksicht auf die Pfeiffer-Meningitis.

1. Die 22 Haemophilus Influenzae Stämme, welche getestet sind, waren alle empfindlich gegenüber Chloramphenicol.

2. Mit einer Dosierung von ca 100 mg Chloramphenicol pro kg und Tag per os wird ein etwa 20—60 mal höherer Chloramphenicolgehalt im Liquor erreicht, als der Empfindlichkeit der von Meningitisfällen gezüchteten Haemophilus Influenzae Stämme entspricht.

3. 13 Fälle von Haemophilus Influenzae-Meningitis, deren Durchschnittsalter 15,4 Monate (das jüngste Kind war 3, das älteste 47 Monate) betrug, wurden wie folgt behandelt: 5 nur mit Chloramphenicol: alle geheilt; 1 mit Chloramphenicol und Streptomycin: geheilt; 7 mit Streptomycin, Penicillin und Sulfonamiden: davon 3 geheilt, 3 gestorben, 1 geheilt mit Restsymptomen.

4. Mit Chloramphenicol behandelte Patienten erholten sich rascher als die mit Streptomycin und anderen Mitteln behandelten.

Sobre la actividad del cloramfenicol frente al hemofilus influenzae con especial referencia a la meningitis por b. influenzae.

1. Sobre 22 cepas de hemofilus influenzae que el autor ha investigado todas han sido sensibles al cloramfenicol.

2. Con una dosificación de alrededor de 100 mg. de cloramfenicol por kilo y día por via bucal se obtiene casi de 20—60 veces un contenido

de cloramfenicol en el líquido cefaloraquídeo que el de la sensabilidad para las cepas de h. influenzae cultivadas de casos de meningitis.

3. En 13 casos de meningitis por h. influenzae cuyo promedio de edad era de 15,4 meses siendo el mas joven de 3 y el mayor de 47 meses que fueron tratados de la manera que sigue se obtuvieron estos resultados: 5 tratados solo con cloramfenicol curaron todos. Uno tratado con cloramfenicol y estreptomicina también curó. 7 tratados con estreptomicina penicilina y sulfapreparados 3 de ellos curaron, 3 murieron y uno curó con secuelas.

4. Los pacientes tratados con cloramfenicol generalmente curan mas deprisa que aquellos tratados con estreptomicina u otras drogas.

Addendum

Since 21.11. 1951 two IM cases have been treated with chloramphenicol in the same way as described above. One was a boy, aged 2 1/2 years, who was unconscious for three days and showed not more than 0.014 % glucose in the spinal fluid. The other was a five months old infant and his illness has been classified as medium. The former was discharged with a slight spasticity of the left leg, and the latter in full health.

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FROM THE CHILDREN'S HOSPITAL (HEAD PROFESSOR A. YLPPÖ, M.D.) AND FROM THE II WOMEN'S HOSPITAL (DEPUTY HEAD H. ZILLIACUS, M.D.) THE UNIVERSITY OF HELSINKI, FINLAND.

Intravascular Red Cell Aggregation in Newborn Infants with Infections

by

T. ARAJÄRVI and H. ZILLIACUS

Introduction

Thanks to a method worked out by KNISELY, BLOCH, ELIOT and WARNER for the direct observation of the blood stream in small blood vessels, it is known that 1) intravascular aggregation of the circulating red blood cells takes place immediately in vessels running through, or close to, tissue subjected to a mechanical trauma, and 2) in many conditions diverging from the normal, such as infections, malignancy, pregnancy, and so on, the circulating red cells are clumped together into aggregates of varying sizes, shapes and rigidity. A displacement of the plasma proteins in the direction of coarse dispersity has been correlated by FÅHRÆUS with the aggregating tendency and increased sedimentation rate of the red cells.

KNISELY and his collaborators repeatedly observed red cell aggregation in connection with various types of generalized infection, especially malaria. In their investigations, which were carried out with a stereo-microscope at 40—100 × magnification, the blood stream in the conjunctival vessels was studied. It was noted in chronic polyarthritis that the degree of intravascular red cell aggregation in the vessels showed a more correct relationship to the other symptoms than the sedimentation rate (LAINE and ZILLIACUS). In cases of monocular inflammatory diseases with a normal sedimentation rate, red cell aggregation was ob-

served in the vessels in and around the inflamed area whereas no aggregation occurred in the vessels of the sound eye (ZILLIACUS 1949).

The problem

Previous investigations on intravascular red cell aggregation in connection with generalized and local inflammation have demonstrated that this method of observation furnishes possibilites for diagnosing infection at an early stage, and also that it is possible to follow the course of the infection in a series of tests on one and the same patient.

Seeing that it is often difficult, as we know, to make an early diagnosis of infection in infants during the first hours, days or weeks of life, it seemed as though a study of the intravascular red cell aggregation in the conjunctival vessels might be of assistance when infants were being examined for infection. A series of children with different types of infection were studied in this way during the first days and weeks of life. Fifteen of these cases will be described in some detail here. A large number of healthy babies of varying ages were used as controls. No granulation or aggregation was observed in the blood stream in the small conjunctival vessels or capillaries in these control subjects. In the narrowest vessels, the red cells flowed along in even, unbroken lines, and in the larger vessels the blood stream was smooth and ungranulated.

Technique

The infant's head was fixed in an adjustable cushioned frame, when necessary after the administration of a sedative in the form of a suppository. An eyelid opener was then applied. The eyeball was brightly illuminated. The conjunctival blood vessels were observed through a stereo-microscope at 40—100 × magnification. For the photographic work, a mirror-reflecting camera was fastened to an ordinary microscope tube and an "ultrapak" objective fitted with a ring condensor replaced the objective. Oblique illumination was used when the instrument was focussed for the photographs. A flashlight through the ring condensor was arranged to synchronize with the exposure of the films.

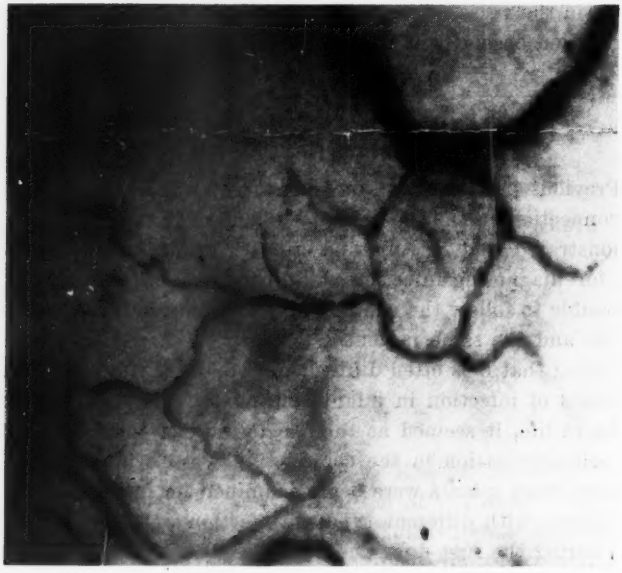

Fig. 1. Intravascular aggregation of the erythrocytes observed in the conjunctival vessels (magnification × 100) of an 8 months old baby suffering from nephrosis, furunculosis and otitis media.

Result of the investigation

Similarly to what has already been observed earlier in connection with different forms of infection in infants, aggregation of the circulating red cells was definitely present in the fifteen cases described here. The oldest child in the series was 8 months old; the ages of the others ranged between 2 and 45 days at the time when the aggregation was observed. For the most part, there was a correlation between the degree of red cell aggregation and the severity of the infection. Definite clumping of the red cells was also observed in cases where the signs of infection were very inconsiderable and difficult for a non-specialist to distinguish. The degree of aggregation was also to a certain extent correlated with the changes in the blood pattern. When the aggregation was strongly marked, the hemoglobin content and the red cell count were often much lower than normal.

Table 1.

Intravascular aggregation of the red cells in 15 cases of infection in newborn babies.

No.	Age	Diagnosis	Degree of red cell aggregation	Blood status at time aggregation was observed		
				Hb	Erythrocytes	Leukocytes
1	8 mths.	Nephrosis, Furunculosis, Supp. otitis med.	+ + +	8.05	3.03	10 600
2	10 days	Cephal hematoma, Intestinal occlusion	+ +	10.65	3.29	27 700
3	5 days	Prematurity, 2 400 g; mild temp.rise 2 090 g; better 2 190 g; better	4/4 + 11/4 ± 16/4 −	18.67	5.13	8 600
4	4 days	Melena neonatorum, Mild temp. rise	+ +	11.20	3.57	11 200
5	38 days	Prematurity, 2 810 g; Pneumonia? 2 890 g; better	13/2 + + 19/2 ±	7.75/64	2.90	8 700
6	45 days	Cong. vit. cord., Ac. gastroenteritis	+	14.10/118	5.18	17 000
7	2 days	Premature twin, 1 740 g; Vomiting, Edema; Better	4/4 + 11/4 ± 16/4 −	15.80/131	4.69	11 700
8	6 days	Ac. Infection	+ +	13.30	3.77	4 900
9	5 days	Prematurity, 1 950 g; Ac. inf. coryza	6/3 − 10/3 + 14/3 ± 31/3 ±	14.8/123	4.52	12 000
10	5 days	Bronchitis, Pneumonia? Cerebral hemorrh., Cong. vit. cord. Death 3 days later	+ +	18.15	4.97	13 300

No.	Age	Diagnosis	Degree of red cell aggregation	Blood status at time aggregation was observed		
				Hb	Erythrocytes	Leukocytes
11	15 days	Acute gastroenteritis Later well	+	18.94/156	5.70	8 600
12	11 days	Prematurity, 2320 g; gen. cond. affected, vomiting Later well	19/3 + 28/3	17.65	4.95	7 400
13	4 days	Ac. infection, vomiting, temp. 39,6° C Later well	+ + +	16.30	4.70	16 000
14	30 days	Prematurity, Gastritis, Pustular rash Later well	+	10.65/89	3.55	8 700
15	7 days	Prematurity, 1800 g; Ulcerous enterocolitis Better	18/4 + + 25/4 ±	14.60 9.47	4.10 2.98	4 200 8 600

Discussion

As intravascular red cell aggregation appears before any other signs of infection have become manifest, this method of examination would seem to be a valuable aid for diagnosing infection at an early stage. As the result of many previous observations (KNISELY *et al.*, ZILLIACUS *et al.*) it is known that the degree of intravascular red cell aggregation is more or less proportional to the increase in the erythrocyte sedimentation rate in cases of generalized infection. In these cases of infantile infection, the red cell aggregation directly observable through the microscope may therefore be regarded as a measure of the sedimentation reaction.

In cases of erythroblastosis foetalis, definite intravascular red

cell aggregation which is in porportion to the blood disturbances caused by the immunization is consistently observed (ZILLIACUS and ARAJÄRVI). This disease, as well as those conditions in which more extensive traumatic lesions (e.g. intracranial hemorrhage following parturition) are present (ZILLIACUS), seem to be the only ones, in addition to infection, where intravascular red cell aggregation occurs in newborn infants.

Summary

The blood stream can be directly observed in the conjunctival blood vessels with the aid of a stereo-microscope at 40—100 × magnification. When this method of observation was applied in a large number of newborn infants during the first days or weeks of life it was noted that the blood stream in the small vessels and capillaries of the conjunctiva was even and ungranulated in completely healthy children. The red cells flowed along in even, single or double lines in both capillaries and paracapillaries. In the larger vessels, the blood stream was even and ungranulated. However, as soon as even very slight prodromal signs of infection appeared, a slight rise in the temperature, a lowering of the general condition, vomiting or abnormality of the stools, for instance, the circulating red cells began to form into clumps. In many cases, aggregation of the red cells was the first sign of infection to appear. The aggregating tendency was more pronounced when the infection was severe than when it was mild. The aggregation phenomenon was characterized by the fact that, in capillaries and paracapillaries, colourless spaces were observable between erythrocyte "carriages" of varying lengths. In vessels of larger calibre the blood stream was granulated. The rate of flow was decreased in all the vessels studied. As it is known from earlier investigations that the degree of red cell aggregation bears a certain relationship to the increased sedimentation rate of the red cells, intravascular aggregation in infants with infection may be regarded as a sedimentation reaction directly observed *in vivo*. Instead of using the microsedimentation reaction an early diagnosis of infection can be made by direct observation of the blood stream with a view to detecting the possible presence of red cell aggregation. This also holds good for premature babies. Cases of erythroblastosis foetalis and cases with extensive traumatic lesions (e.g. parturition injuries) form exceptions to this rule since they also display intravascular red cell aggregation.

Fifteen cases are described.

Agrégat intravasculaire de globules rouges ches les nouveaux-nés porteurs d'infection.

On a étudié chez des nourrissons normaux et des nourrissons atteints d'infection, l'agrégat intravasculaire de globules rouges dans les petits vaisseaux sanguins du conjonctif, selon la méthode de KNISELY et ses collaborateurs. La tendance à s'agréger a été plus prononcée dans les infections sévères que dans celles d'évolution bénigne. L'agrégat intravasculaire de globules rouges peut être considéré comme un test de sédimentation des globules rouges, obtenu directement in vivo.

Intravaskuläre Zusammenballung der roten Blutkörperchen bei infizierten Neugeborenen.

Die intravaskuläre Sedimentierung der roten Blutkörperchen in den kleinen Conjunktivalgefässen wurde nach der Methode von KNISELY u. a. bei normalen Kindern und Kindern mit Infektionskrankheiten studiert. Die Aggregationstendenz war stärker bei ernsten als bei leichten Infektionskrankheiten ausgeprägt. Die intravaskuläre Erythrocytenzusammenballung kann als Blutsenkungsprobe betrachtet werden, welcher direkt in vivo abgelesen werden kann.

Acumulación intravascular de los hematíes en recién nacidos con infecciones.

Se ha estudiado en niños normales y en niños afectos de enfermedades infecciosas el fenómeno de acumulación intravascular de los hematíes en los pequeños vasos conjuntivales de acuerdo con el método de Knisely y colaboradores. La tendencia acumulativa era mas pronunciada en las formas de infecciones severas que en los casos medianos. La acumulación intravascular de los glóbulos rojos puede ser considerada como una prueba de sedimentación globular obtenida directamente in vivo.

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Intravascular Red Cell Aggregation in Erythroblastosis Foetalis

by

H. ZILLIACUS and T. ARAJÄRVI

Sporadic examinations of the blood stream in the conjunctival vessels of Rh-immunized newborn infants according to the method indicated by KNISELY *et al.* showed that clumping of the circulating red cells often occurred (ZILLIACUS and NEVANLINNA 1950). In the present investigation, the intravascular red cell aggregation was observed shortly after birth in 12 Rh-immunized newborn infants. The degree of aggregation was also studied by means of repeated observations both after a blood exchange and in those cases where no exchange of blood was undertaken. A large number of healthy non-Rh-immunized children were used as controls, observations being made with the same technique as in the above-mentioned children immediately after birth and during the first days of life. In healthy children, no granulation or aggregation can be observed in the blood stream in the conjunctival capil laries and paracapillaries. In the finest blood vessels, the red cells run in even, single or double lines; in the larger vessels, the stream is even and ungranulated. This normal picture is, however, obtained only if no silver nitrate solution has been dropped into the eyes after birth, since a reactive conjunctivitis over one or two days causes a mild degree of aggregation.

The same technique was used as described in the previous paper (ZILLIACUS and ARAJÄRVI).

Fig. 1. Intensive intravascular red cell aggregation in the capillaries and paracapillaries of the conjunctiva in an Rh-immunized infant immediately after birth. Hb 6.1 g %. Red blood cells 1.35 mill. Erythroblasts 386/100. Blood exchange after the picture was taken.

Case Reports

Case 1. (Record no. 3695.) Two other children, born 1947 and 1950, were healthy. Patient was born Oct. 3, 1951 at 13.20 hrs by Cesarean section. Male, birth weight 3 430 g, height 49 cm. Lively at birth. Hb 6.1 g %. Red blood cells 1.35 mill. Erythroblasts 386/100. Meulengracht's test 1:125. Blood group A Rh positive. Coomb's test + +. Aggregation + + + (Fig. 1). Rapid deterioration and increasingly severe jaundice. Blood exchange between 17.15 and 18.15 hrs, resulting in an improvement. Oct 4: Hb 19.65 g %, R.B.C. 7.40 mill. — Oct. 5: Hb 18.15 g, R.B.C. 6.65 mill., aggregation + (Fig. 2). — Oct. 8: Hb 16.80 g, R.B.C. 5.66 mill., aggregation — (Fig. 3). — Oct. 12: Jaundice less pronounced. — Oct. 23: Skin no longer yellow, infant better.

Case 2. (Record no. 3527.) Four other children had died 1—2 days after birth. Mother Rh negative, antigens +. Spontaneous delivery Sept. 21, 1951. Female, birth weight 2 890 g, height 46.5 cm. Hb 10.30 g.

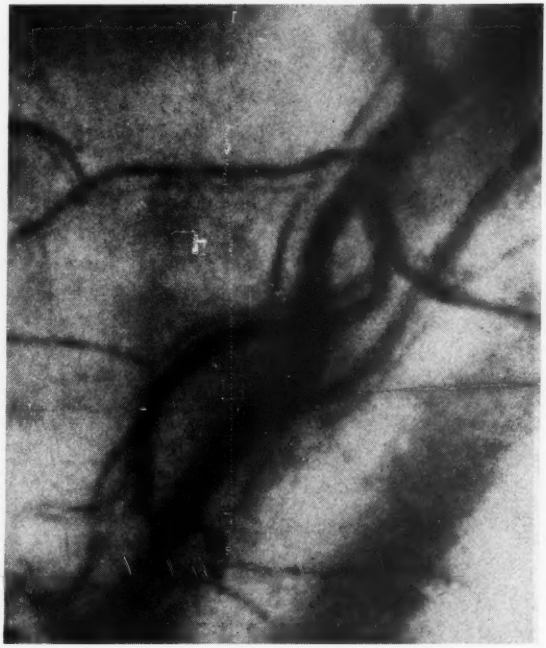

Fig. 2. Same case, 2 days later. The aggregation is considerably reduced. Hb 18.15 g %. Red blood cells 6.65 mill.

R.B.C. 2.64 mill. Erythroblasts 492/100. Meulengracht 1:26. Blood group B Rh positive. General condition poor, skin yellowish. — Sept. 22: A blood exchange, Hb 20.29 g, R.B.C. 6.68 mill. — Sept. 25: Hb 18.94, R.B.C. 6.40 mill. — Sept. 36: Aggregation ±. — Oct. 4: Patient better.

Case 3. (Record no. 3662.) The mother had had two healthy children with her first husband. With the second, one living and 4 dead or stillborn icteric children. Spontaneous delivery Sept. 28, 1951. Male, birth weight 3 670 g, height 50 cm. Deeply jaundiced. Liver palpable 2 fingers' breadth below costal margin. — Oct. 1: Hb. 9.47 g, R.B.C. 2.58 mill, erythroblasts 10/100. — Oct. 2: Hb 12.47 g, R.B.C. 3.43 mill., aggregation + +. — Oct. 5: Hb. 10.47 g, R.B.C. 2.80 mill. — Oct. 20: Hb 9.00 g, R.B.C. 3.02 mill., practically no jaundice.

Case 4. (Record no. 3667.) The mother had had one healthy child. Another died of jaundice when 2 $^1/_2$ days old. Mother Rh-immunized.

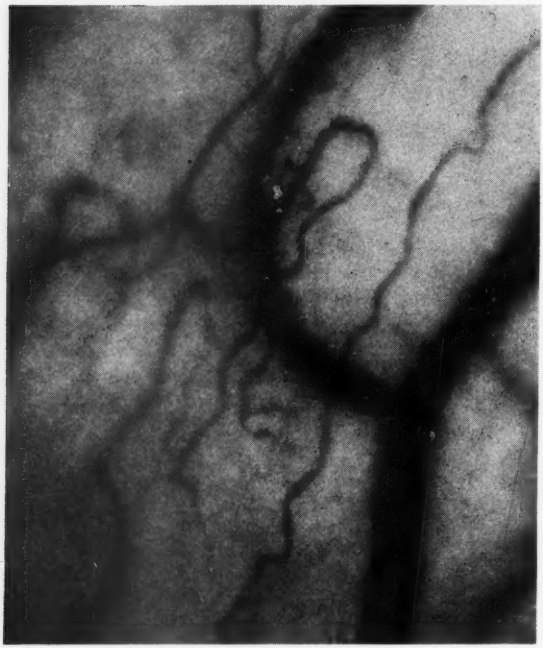

Fig. 3. Same case after a further 3 days. No signs of aggregation. Hb 16.80 g %. The infant was better, and all signs of yellowness had disappeared.

Spontaneous delivery Oct. 1, 1951 at 19.45 hrs. Male, birth weight 3 350 g, height 50 cm. General condition fairly good. Hb 12.45 g, R.B.C. 3.10 mill., erythroblasts 9/100. Meulengracht 1:38. Blood group A Rh positive. Coomb's +. Aggregation + + +. At 22.45 hrs, an exchange of blood. Oct. 15: Infant better.

Case 5. (Record no. 1733.) The mother had previously given birth to 2 live infants, at normal deliveries. Blood group A Rh negative, immunized. Spontaneous delivery Apr. 21, 1951. Female, birth weight 3 750 g. Blood group 0 Rh positive. Hb 20.02 g, R.B.C. 5.86 mill., erythroblasts 12/100. Aggregation + +. Apr. 22: No more jaundice.

Case 6. (Record no. 3483.) The mother had previously had 3 children, 2 of which had died of jaundice immediately after birth; Rh-immunized. Caesarean section Sept. 18, 1951 at 15.00 hrs. Male, birth weight 3 100 g, height 50 cm. Hb 12.25 g, R.B.C. 3.78 mill. Erythroblasts 5/100. Meule-

gracht 1:12. Blood group A Rh. positive. Aggregation + +. Sept. 28: Jaundice improving. — Oct. 19: Infant better.

Case 7. (Record no. 1276.) Mother had had 1 healthy infant and 1 abortion, Rh negative, immunized. Spontaneous delivery Mar. 17, 1951. Female, birth weight 3 410 g, deeply jaundiced. Hb 8.40 g, R.B.C. 2.92 mill., erythroblasts 4/100. Meulengracht 1:9. Blood group Rh positive. — Mar. 19: Hb 12.87 g, R.B.C. 3.89 mill. Aggregation + + +, no blood exchange. — Mar. 20: Infant better, and on Mar. 28: Hb 11.20 g, R.B.C. 3.50 mill. Aggregation—. — Apr. 4: No jaundice, Hb 11.00 g, R.B.C. 3.20 mill. Infant better.

Case 8. (Record no. 652.) Mother had had 2 healthy children and 2 abortions, 0 Rh negative, immunized. Coomb's +. Spontaneous delivery Jan. 31, 1951. Male, birth weight 3 730 g, Hb 13.50 g, R.B.C. 3.91 mill., erythroblasts 9/100, Meulengracht 1:90, aggregation +. — Feb. 5: Hb 18.15 g, R.B.C. 5.20 mill., aggregation ±. — Febr. 6: Aggregation —, and on Feb. 9: Infant better. Hb 17.65 g, R.B.C. 4.99 mill.

Case 9. (Record no. 863.) Mother had had 3 healthy children, Rh negative, immunized. Spontaneous delivery Feb. 15, 1951. Female, birth weight 3 860 g, height 51 cm, Hb 13.30 g, R.B.C. 3.41 mill., erythroblasts 21/100, blood exchange. — Feb. 20: Hb. 16.80 g, R.B.C. 5.94 mill., aggregation—, infant better.

Case 10. (Record no. 1205.) Mother had had 2 healthy children, 2 newborns had died of jaundice, 1 abortion, Rh negative, immunized. Spontaneous delivery Mar. 12, 1951. Female, birth weight 4 440 g, jaundiced, Hb 12.65 g, R.B.C. 3.75 mill., erythroblasts 17/100, Meulengracht 1:21, aggregation + +, blood exchange. — Mar. 19: aggregation +. — Mar. 28: Infant better, aggregation ±. — Mar. 30: Hb 12.65 g, R.B.C. 4.80 mill.

Case 11. (Record no. 1169.) First child delivered spontaneously at home, Feb. 20, 1951. Hospitalized because of increasingly severe jaundice. Mother Rh negative, immunized. Mar. 13: Hb. 4.95, R.B.C. 1.49 mill., aggregation + + + +, blood transfusion several times. — Mar. 19: Aggregation +. — Mar. 20: Hb. 13.75 g, R.B.C. 4.77 mill. — Mar. 28: Hb 10.0 g, R.B.C. 3.73 mill., aggregation ±.

Case 12. (Record no. 1177.) Mother Rh negative, immunized. First child spontaneously delivered Mar. 10, 1951. Female, birth weight 4 170 g, Hb 14.6 g, R.B.C. 4.80 mill., erythroblasts 1/100, no blood exchange. — Mar. 13: Aggregation +. Mar. 17: Infant better, Hb 20.90 g, R.B.C. 6.01 mill.

Results

In 10 cases of erythroblastosis fetalis (Nos. 1, 3, 4, 5, 6, 7, 8, 10, 11, 12) definite red cell aggregation was observed immediately after birth and during the first days of life. The aggregation was very marked in those cases where a high degree of iso-immunization was present (No. 1, Fig. 1; nos. 4, 7, 11). In the capillaries and paracapillaries, long colourless spaces were observed between the erythrocyte "carriages," and the rate of flow was considerably reduced. The rate of flow was also reduced in the paracapillaries and larger blood vessels and large clumps of red cells moved about in these vessels. In other cases where the immunization was of a lesser degree the aggregation was also very distinct, although it was less pronounced than in the afore-mentioned cases.

An exchange of blood was effected in 4 cases (nos. 1, 2, 4 and 11). Observation of the aggregation before and after the blood exchange revealed that it decreased in intensity as the condition improved, as shown in Figs. 1—3. There seemed in general to be a certain amount of correlation between the degree of red cell aggregation and the infant's general state of health, the severity of the jaundice and the specific blood changes.

Discussion

The nature of this intravascular aggregation is obscure. The instantaneous aggregation of the red cells that takes place on an injury to the tissue is thought by KNISELY and co-workers to be due to the fact that the red cells become enveloped in a sticky membrane, which is formed by substances liberated through the action of trauma. The aggregation mechanism in infections, malignancy, pregnancy, and so on, which manifests itself in the form of an increased sedimentation rate, is correlated, to a certain extent at least, with disturbances in the composition of the plasma proteins (FÅHRÆUS), although other causes may also exist simultaneously. In the case of intravascular aggregation of the erythrocytes resulting from iso-immunization, as in erythro-

blastosis foetalis, the ordinary clumping mechanism of iso-immunization is presumably, in part at least, the cause of the aggregation.

The intravascular aggregation observed immediately after birth in the case of erythroblastosis foetalis makes it possible to diagnose Rh-immunization without having recourse to a serologic examination. Intravascular aggregation immediately after birth has, in fact, not been observed in any category other than Rh-immunized children except in cases of severe traumatic lesions at this age.

The obvious correlation between low hemoglobin and red cell values and the degree of red cell aggregation may possibly be associated with KNISELY's observation that aggregated red cells to a large extent undergo phagocytosis.

It seems logical, also, to correlate a number of typical histologic changes in the placenta and the infant's liver with the occurrence of red cell aggregates, which may be likened to microemboli.

Summary

The blood stream in the small conjunctival vessels was observed in twelve cases of erythroblastosis foetalis with the aid of a stereoscopic-microscope immediately after birth. Intravascular red cell aggregation was observed in all the immunized infants. No aggregation was observed in healthy newborn infants. The correlation between the blood values in the child and the degree of aggregation was such that, when the aggregation was pronounced the red cell and hemoglobin values were low. After a blood exchange, or in connection with a spontaneous improvement in the state of health, the red cell aggregation decreased proportionally as the blood values improved.

The diagnostic and clinical significance of these observations is discussed.

Agrégat intravasculaire des globules rouges dans l'érythroblastose foetale.

Le courant sanguin dans les petits vaisseaux du conjonctif a été observé dans douze cas d'érythroblastose foetale, à l'aide d'un stéréomicroscope, immédiatement après la naissance. Un agrégat intravasculaire de globules rouges a été observé chez tous les nourrissons immunisés.

Par contre, on n'en a pas observé chez les nouveaux-nés sains. La corrélation entre les chiffres sanguins chez l'enfant et le degré d'agrégat était telle, qu'à un agrégat prononcé correspondait un chiffre de globules rouges et d'hémoglobine bas. Après transfusion sanguine, ou en relation avec une amélioration spontanée de l'état de santé, on observe que l'agrégat de globules rouges diminue dans la mesure où les valeurs sanguines s'améliorent. On discute le diagnostic et la signification clinique de ces observations.

Intravaskuläre Zusammenballung der roten Blutkörperchen bei foetaler Erythroblastose.

Der Blutstrom in den engen Conjunktivagefässen wurde in 12 Fällen von foetaler Erythroblastose mit Hilfe eines Stereomikroskopes unmittelbar nach der Geburt beobachtet. Eine Zusammenballung roter Blutzellen wurde bei allen Rh-immunisierten Kindern festgestellt. Bei gesunden Neugeborenen wurde keine Zusammenballung beobachtet. Die Beziehungen zwischen den Blutwerten des Kindes und dem Ausmass der Aggregation waren folgendermassen: Wenn die Zusammenballung ausgeprägt war, lagen die Erythrocyten- und Hämoglobinwerte niedrig. Nach Blutaustausch oder in Verbindung mit spontanen Besserungen des Zustandes nahm die Erythrocytenzusammenballung in demselben Masse ab als die Blutwerte sich besserten. Die diagnostische und klinische Bedeutung dieser Beobachtungen wird diskutiert.

Acumulación intravascular de los hematíes en la eritroblastosis fetal.

En 12 casos de eritroblastosis fetal se ha examinado la corriente sanguínea de los vasos pequeños conjuntivales por medio del estereomicroscopio inmediatemente después del nacimiento. En todos los casos de isoinmunización pudo observarse una acumulación intravascular de los hematíes, fenómeno que no se producía en los recién nacidos normales. La correlación entre los valores sanguíneos del niño y el grado de acumulación de los hematíes era tal, que cuando el grado de acumulación era muy pronunciado los valores de glóbulos rojos y hemoglobina eran bajos. Tras la exsanguíneo-transfusión o en relación con la mejoria expontánea de la enfermedad el grado de acumulación de los hematíes disminuía en la proporción que los valores sanguíneos mejoraban. Se discute el diagnóstico y la significación clinica de estas observaciones.

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CASE REPORTS

Re-Infections with Measles

Familial Immunity Defect

by

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In the case of the virus infections of childhood the immunity after disease is massive. Indeed, most text-book authors state that in the case of measles and chicken pox it is an absolutely life-long immunity. As far as mumps and German measles are concerned, the authors, as a rule, make some reservations.

Especially in the earlier medical literature on the subject there are numerous communications about patients who have had measles twice or several times. However, these reports should be regarded with the greatest caution, as most of them are based upon anamnestic information. Undoubtedly such cases have often been wrongly diagnosed. Atypical cases of German measles and scarlet fever, and also of drug eruptions, perspiration eruptions and the skin rashes of vaccination are among the possible causes of diagnostic error.

In measles two or more eruptions at short intervals may be observed in many cases. In 1932 K. LAU (5) reported the cases of two children of the same family who both developed a secondary eruption 10 days after the first had subsided. In 1940 HÄNTZSCHEL (3) observed secondary eruptions in four patients, appearing, respectively, 6, 21, 22 and 23 days after the first eruption. In 1919 SALZMANN (6) reviewed 68 cases from the literature in which the second eruption appeared within 100 days after the first; 61 of these appeared within 6 weeks. It is open to discussion whether these secondary cases are recurrences or actual re-infections. Considering the fact that so many of them occur very early after the first infection, it would seem to be most probable that they are recurrences.

At the present time, the diagnosis of measles still has to be established on a purely clinical basis. The demonstration of the virus cannot be used as a clinical diagnostic aid, and no one has managed to demon-

strate specific seroreactions in the blood of the patients after recovery from the disease.

In 1914 FRIEDJUNG (1) established the following criteria for a case to be recognized as a fresh infection with measles:—

(1) The diagnosis will have to be supported by either information about infection from unquestionable cases of measles, or transmission of the contagion from the patient to unquestionable cases of measles.
(2) The prodromal stage and the symptoms must have developed distinctly.
(3) Both cases should preferably have been diagnosed by the same examiner.

When the cases reported in the literature which do not comply with these demands are left out of consideration, a considerable number still remain. In 1919 SALZMANN (6) had collected 36 cases. However, she modified FRIEDJUNG's last demand in such a manner that the diagnosis in each case could be made by the same examiner or by authentic witnesses.

Cases of 3 or 4 infections with measles are reported with striking frequency. SALZMANN thus found 21 communications about 3 and 2 about 4 infections in the same patient. Further, it is noteworthy that such cases are frequently of familial occurrence (8 cases in SALZMANN's series). In HOLT's "Diseases of Children" (2) SAMUEL KARELITZ states that he has observed measles twice in 5 children of the same family, the second infection occurring 6 years after the first.

In a more recent publication of 1950 KARELITZ (4) discusses the immunity after abortive cases of measles in order to estimate the effect of gamma-globulin and convalescent serum. He sent out questionnaires to a number of 500 paediatricians, of whom 166 replied. Further he discussed the problem with 500 paediatricians, at a congress. It was stated by 19 that they had observed measles in 29 patients who had previously had abortive types of the disease. Six stated that they had observed regular cases of measles twice in the same patient. Four had seen multiple cases of familial occurrence.

Re-infections with measles are undoubtedly very rare. However, the reports mentioned seem to indicate that there are people whose immunization power against the disease is very poor, and that in some cases this defect is a constitutional hereditary characteristic.

In Blegdamshospitalet we have observed a case of presumably fourth infection with measles.

The patient was an 8-year-old boy (case record No. 2013/50) who was hospitalized from March 31st to April 27th, 1950. According to his mother's statements, he had had measles 3 times before (at the ages of 2, 4 and 6 years). On each occasion the disease had been diagnosed

by a specialist in paediatrics. On all three occasions the boy had had a vigorous eruption and had run a high temperature. His mother did not remember anything about the prodromal symptoms. When the boy was ill the second and third times his brothers and sisters were also ill with the same symptoms. On each occasion the disease had occurred at times when there was an epidemic of measles. The patient had had whooping cough twice (when 1 $^1/_2$ and 6 years old), both times diagnosed by a paediatrician and secured by growth of whooping cough bacilli in the special dish. He had had German measles twice (at ages of 2 and 4 years), had often had tonsillitis, had had "influenza" several times, but never chicken pox or mumps.

Present disease: For a week before admission the child had been febrile, with rising temperature, and had had cough, coryza and headache. During the last few days there had been vomiting and diarrhoea. The day before admission an eruption with large macules appeared. On admission to hospital the patient was highly febrile, and his general health was affected. He had catarrhal symptoms, conjunctivitis and a typical morbillous eruption which was universal, with large macules and partly haemorrhagic. The temperature fell in the course of 3 days. The eruption subsided in the course of 9 days. No complications.

The patient's *familial anamnesis* was as follows: His *mother:* Had had measles when she was 7 and 37 years old (the second time barely 2 weeks after the patient's present disease). She distinctly remembered the first infection, as several sisters and brothers were ill simultaneously. They had had photophobia and a very pronounced eruption. She had had the other infections of childhood, except chicken pox, only once. The patient's *father:* Did not accurately recall his diseases of childhood, but had at any rate not been affected by any of them more than once. *Mother's sisters and brothers* (5 in all): The two youngest were said to have had measles two or three times. *A brother* (6 years old): Had measles twice (when 2 and 4 years old), both times simultaneously with the patient, but not ill during the patient's present disease. Whooping cough twice (whooping cough bacilli demonstrated on both occasions), one of the attacks simultaneously with the patient. *A brother* (2 years old): Had measles once (during the patient's present disease). Whooping cough once, at the age of 10 months.

By means of determination of the patient's serum proteins and by examining the content of antibodies in his blood before and after vaccinations we attempted to demonstrate a failing antibody-formation.[1]

The total protein content in the plasma was 6.1 per cent, albumins 3.9 per cent and globulins 2.2 per cent. The electrophoretic pattern also

[1] The electrophoretic examinations were made by Dr. Niels Harboe, the University Institute of General Pathology, Copenhagen. Determinations of antibodies and seroreactions were made at Statens Seruminstitut.

showed a normal distribution of the serum proteins, in particular the content of gamma-globulin was normal.

Diphtheria antitoxin content < 0.01 A. U./ml. Tetanus antitoxin content < 0.001 A. U./ml (the patient had not been vaccinated against diphtheria or tetanus). Parotitis complement fixation < 4 (the patient had not had mumps). Antibodies against influenza: Haemagglutination inhibition > 128 influenza A, < 2 influenza B. Complement fixation: < 2 influenza A, < 2 influenza B. The patient had thus formed antibody against influenza A.

On April 15th, 1950, the patient was vaccinated with diphtheria and tetanus anatoxins. Two weeks later electrophoretic examination of his serum showed no distinct changes of the proteins, and diphtheria or tetanus antitoxin could still not be demonstrated in the blood (which could not be expected either after so short a period). On May 15th, 1950, the second diphtheria vaccination was made. Two weeks later considerable amounts of antitoxin were demonstrated in the patient's blood: Diphtheria antitoxin: 1.25 A. U./ml. Tetanus antitoxin: 0.42 A. U./ml. The electrophoretic pattern still showed no distinct changes.

On June 6th, 1951 (12—13 months after the second and before the third vaccination), the content of diphtheria antitoxin was 0.14 A. U./ml, the tetanus antitoxin content being 0.08 A. U./ml (normal conditions [7]). During the past year the patient had had no fresh infections.

Discussion

It may, of course, be doubted whether the patient whose case has been reported here has had measles several times, as we have not observed the three previous infections, but the anamnestic information is highly indicative thereof. On each occasion the disease occurred in the course of an epidemic, and the last three times there had been several cases in the family. The disease had each time been diagnosed by a paediatrician. The familial occurrence of the phenomenon, and the lowered resistance to other infectious diseases are indicative of a poor immunization capacity. The examinations of the patient's serum proteins and the formation of antibodies after vaccination against diphtheria and tetanus showed normal conditions. However, this need not mean that the patient's power of immunization against all infections is normal. Further, it is possible that he loses his antibodies abnormally soon. Still, the content of diphtheria and tetanus antitoxins was normal a year after the second vaccination. It is known that the immunity in measles is attached to the gamma-globulin fraction of the serum proteins. No rise of the gamma-globulin content was demonstrated in the 3 electrophoretic examinations. However, experience also shows that in many infections antibodies of clinical importance are produced in quantities

which are too small to cause any visible changes in the electrophoretic diagram. The rise of the content of diphtheria and tetanus antitoxins demonstrated did not cause any demonstrable changes either in the electrophoretic pattern.

Summary

Authentic communications about re-infections with measles are rare. The writer reports a case of presumably fourth infection with measles in an 8-year-old boy who had also had whooping cough and German measles twice, and, further, recurring tonsillitis and "influenzal infections". The patient's mother, 2 of her sisters and brothers, and a brother had had measles twice, the brother also whooping cough twice.

Examinations of the patient's serum proteins showed a normal content of total protein, albumin and globulin. The electrophoretic pattern was normal. Diphtheria and tetanus antitoxins could not be demonstrated in the patient's blood. Parotitis complement fixation < 4. Antibody against influenza A could be demonstrated. After vaccination against diphtheria and tetanus a normal formation and excretion of antitoxins was ascertained (followed for a year). The electrophoretic pattern remained unchanged. Previous communications and the anamnestic information received about this patient seem, however, to indicate that there are individuals who have a poor immunization capacity against measles (in this patient also against certain other infections), and that this is a constitutional hereditary property.

Récidives de rougeole. Immunité familiale défectueuse.

Les communications authentiques de cas de réinfection de rougeole sont rares. L'auteur rapporte le cas d'un garçon agé de 8 ans qui présenta successivement 4 rougeoles et 2 fois la cocqueluche et la rubéole et de plus des angines et grippes à répétitions. La mère du malade, deux de ses frères et sœurs et un frère du malade ont eu deux fois la rougeole, le dernier ayant de plus la coqueluche égalemant deux fois.

L'examen des protéines sériques du malade montra des chiffres normaux de protéines totales, d'albumine et de globuline. L'électrophorèse était également normale. Les antitoxines diphtérique et tétanique ne purent être mises en évidence dans le sang du malade. La fixation du complément parotidien se montra au dessous de 4. Des anticorps contre l'influenza A furent trouvés. A la suite d'une vaccination contre la diphtérie et le tétanos, on constata que la formation et l'excrétion d'antitoxines suivies durant une année était certaine. La courbe d'éléctrophorèse resta cependant inchangée. Les communications retrouvées dans la littérature de même que l'histoire clinique de ce cas, semblent indiquer, cependant, qu'il existe des individus qui sont doués d'une très

faible capacité d'immunité contre la rougeole (et chez notre malade, également contre d'autres affections) et qu'il s'agit là d'une propriété constitutionnelle et héréditaire.

Wiederansteckungen mit Masern. Immunitätsmangel in der Familie.

Berichte über autentische Wiederansteckung mit Masern sind selten. Der Verfasser beschreibt einen Fall von vermutlich vierter Wiederansteckung mit Masern bei einem 8-jährigen Knaben, welcher auch Keuchhusten und Röteln zweimal, und weiterhin wiederkehrende Mandelentzündung und "Grippeninfektionen" gehabt hatte. Die Mutter des Patienten, 2 ihrer Geschwister und ein Bruder des Patienten hatten Masern zweimal, der Bruder auch Keuchhusten zweimal gehabt.

Untersuchungen des Serumproteins beim Patienten wiesen normalen Gehalt an Totaleiweiss, Albumin und Globulin auf. Die elektrophoretischen Werte waren normal. Die Anwesenheit von Diphtherie- und Tetanusantitoxinen konnte im Blute des Patienten nicht nachgewiesen werden. Die Parotitis-Komplementenbindung < 4. Grippenantikörper A konnten nachgewiesen werden. Nach Impfung gegen Diphtherie und Tetanus wurde eine normale Bildung und Ausscheidung von Antitoxinen ermittelt (kontrolliert ein Jahr lang). Die elektrophoretischen Werte blieben unverändert. Frühere Mitteilungen und die anamnestischen Angaben über diesen Patienten scheinen jedoch hinzuweisen, dass es Personen gibt, welche eine mangelhafte Immunität gegen Masern besitzen (bei diesem Patienten auch gegen gewisse andere Ansteckungen) und dass dies eine konstitutionelle, erbliche Eigenschaft sei.

Reinfecciones sarampionosas. Defecto inmunitario familiar.

Casos de verdadera infección por sarampión son muy raros. El autor comunica un caso de posible cuarta infección por sarampión en un niño de 8 años el cual había tenido también la tos ferina y rubeola dos veces y además tonsilitis recurrentes e "infecciones tipo influenza". La madre del enfermo y dos de sus hermanos y hermanas así como un hermano del niño habían padecido el sarampión dos veces y en dicho hermano también la tos ferina había sido doble. El examen del suero del enfermo mostraba un contenido normal de proteinas totales y de las fracciones albúmina-globulinas. El examen electroforético daba valores normales. No pudo hallarse en la sangre del niño antitoxinas diftérica y tetánica. La fijación del complemento para la parotiditis era < 4. Pudo demostrarse anticuerpos frente a influenza A. Tras ser vacunado con las vacunas antidiftérica y antitetánica se produjo una normal formación y eliminación de antitoxina (seguida durante un año). Los valores electroforéticos no variaron. Por los datos anamnésicos parece deducirse la

existencia de un defecto en el sentido de una pobre capacidad de inmunidad frente al sarampión (y en este caso también frente a otras infecciones), siendo ello de naturaleza constitucional hereditaria.

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A Case of the Hand-Schüller-Christian Disease Treated with Cortisone[1]

(A Discussion of the Primary or Secondary Nature of the Lipoid Deposits)

by

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Although the clinical picture of the Hand-Schüller-Christian disease is familiar, a report of the present case appears warranted for the following three reasons. Firstly, cases in which all the classical symptoms are well developed are relatively uncommon. Secondly, experience with cortisone therapy is as yet limited. Finally, the case throws some light on the controversial question of whether the lipoidosis is primary or whether it is secondary to some tissue injury which favours the deposit of lipoids.

[1] The case was presented at the exhibition of the tenth Northern Pediatric Congress, Stockholm, in 1951.

The treatment of the disease has hitherto been tentative. Among the forms of therapy have been diet, irradiation, splenectomy and the administration of thyroid or pituitary hormone extract. None of them has proved effective. The adrenocortical hormone not only influences the metabolism of fats, but also has a generally stimulating effect on the tissues. Moreover, good results have been obtained with ACTH or with the adrenocortical hormone in other diseases in which the reticuloendothelial system is involved. It would therefore appear logical to use cortisone therapy in the disease in question.

Case Report

The patient was a boy, born in November 1948; birth weight 3200 g. His parents lived together but were unmarried. His mother had had asthma as a child; there was nothing else of interest in the family history.

The patient's general health and development had been normal until July 1950, when he contracted whooping cough. At the end of August, his temperature was between 38 and 40°C for several days; he was subsequently tired and fretful and did not seem himself. He was admitted to the Hospital at Hudiksvall at the end of September; he then had small, punctate, reddish-brown discolorations on the skin. Icterus developed about September 22. On October 12, the liver was palpable almost to the level of the umbilicus; 10 days later splenomegaly was noted. On Jan. 24, 1951, protrusion of the left eyeball was observed. On February 4, the first signs of necroses appeared in the palate; they subsequently became increasingly severe. Shortly after their appearance, polyuria and polydipsia developed.

In the middle of February, the patient was sent to Kronprinsessan Lovisa's Hospital for Children. Examination on admission showed the following; pronounced icterus, increased hairiness of the entire body, and numerous, reddish-brown, crusted papules over practically the whole body. There was also protrusion of the left eyeball, moderate swelling of the soft tissues in the left temporal region and extensive, foul-smelling necroses in the palate and gingivae. The liver was palpable four finger-breadths below the costal margin, the spleen was moderately enlarged; the superficial lymph nodes were only slightly enlarged.

Roentgenograms of the skull showed a round defect, about 2 $^1/_2$ cm in diameter, in the frontal bone and a similar, more diffuse thinning of the bone towards the base of the skull and the orbit. *Roentgenograms of the long bones* revealed only a coarse and somewhat patulous trabeculation pattern.

Blood analyses. The haemoglobin count was between 11.2 and 12 g per cent; R.B.C. 3.6—3.8 million per mm^3. W.B.C. and differential

Fig. 1. The patient, shortly after admission to Kronprinsessan Lovisa's Hospital for Children.

count were within normal limits; thrombocytes 70,000—187,000. The prothrombin index, bleeding time and coagulation time were normal. Serum cholesterol 140—217 mg per 100 cc. Meulengracht 1 : 70. The Takata reaction was negative. The serum protein values, both total proteins and the albumin-globulin ratio, were within normal limits. W. R. negative.

Urine analyses. With unrestricted fluids, approximately 2 liters of urine, with a specific gravity of 1.006—1.007, were excreted per 24 hours. Tests for albumin and sugar were negative and nothing abnormal was found in the sediment. Repeated determinations of the 17-ketosteroids gave values between 1.3 and 2.9 mg per 24 hours.

Biopsy of the skin lesions showed oedema and vacuolization of the epithelial cells of the epidermis. No foam cells, eosinophil cells or granuloma cells were visible. *Tibial puncture* showed the bone marrow to be toxic; the picture possibly substantiated a diagnosis of lipoidosis. *Splenic puncture:* the reticulo-endothelium was markedly hyperplastic; there were numerous, large agglomerations of cells including phagocytes (phagocytosis of hemoglobin and lipoids). *Puncture of the defect in the frontal bone:* the reticular tissue was notably hyperplastic and contained plentiful lymphocytes. Numerous phagocytes, of the same type as those in the spleen, were also present.

The splenic puncture and aspiration of the defect in the skull made it possible to establish a diagnosis of the Hand-Schüller-Christian disease. On the other hand, the skin lesions did not present a picture typical of

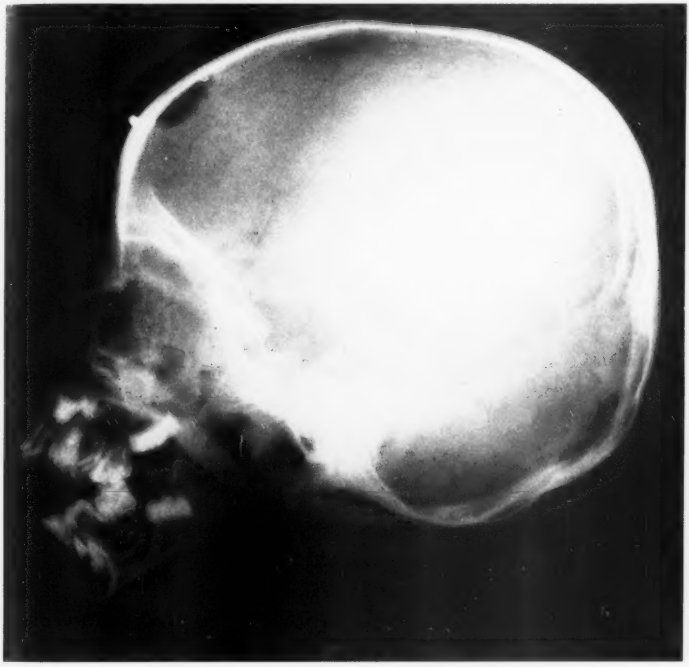

Fig. 2. Roentgenogram of the skull. Note the distinct defect in the frontal bone.

this disease with lipoid phagocytosis. This fact indicates that the lipoid deposits are not to be regarded as primary, but as secondary to the tissue lesions.

Cortisone therapy was started on April 5, 1951; the dose given was 3 mg per kg of body weight, injected intramuscularly once a day. Even after a few days the patient improved noticeably. He became livelier, the protrusion of the eyeball became less evident and the liver and spleen decreased rapidly in size. Unfortunately, after just over a week's treatment, oedema developed and increased successively. No changes were found in the chemistry of the blood, nor did an ECG show any signs of potassium deficiency. There was no longer any polydipsia and the daily volume of urine was normal. Since oedema became massive, cortisone therapy was discontinued on April 25. A rapid exacerbation took place in the patient's condition and he died on May 1.

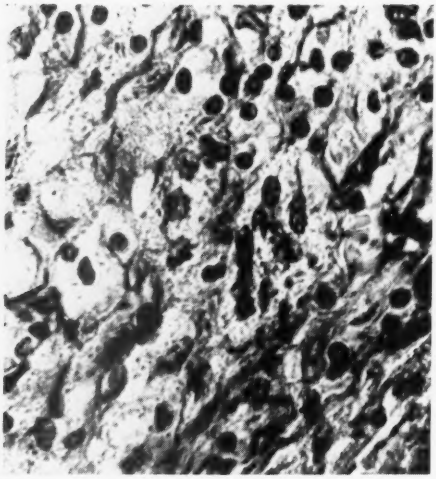

Fig. 3. Section through the granulation tissue from the left orbit. Typical, large, pale cells are very distinct.

Autopsy[1]

The lungs were of firm consistency and poorly aerated. The parenchyma was reddish-blue, extremely tough and fibrous with a diffuse infiltration of greyish, firmer streaks. The bronchi yielded some tenacious, mucopurulent plugs. A number of somewhat firm, pink glands, the size of small beans were present in the hilum. Microscopic examination showed bronchitis and capillary bronchitis, as well as lesions typical of the Hand-Schüller-Christian disease with lipoid phagocytizing giant cells with positive stainability for fat and cholesterol.

The spleen was extremely enlarged and weighed 175 g (normal weight for the age 43.5—46 g); it was soft, reddish-brown and brittle. The parenchyma was loose in consistency, with scattered, greyish-white, firmer nodules. Microscopic examination showed numerous reticular cells with plentiful, granulated cytoplasm. A number of multinuclear cells were also present. There was no affinity for fat stains.

The liver was moderately enlarged, its weight being 550 g (normal weight for the age 428—484 g). The surface was finely granular. The

[1] Valuable help was obtained from the Dept. of Pathology (Director: Prof. WILTON) of Karolinska Institutet both in carrying out the autopsy and in assessing the specimens.

parenchyma was dark green, extremely tough and firm, with large quantities of fibrous streaks. The cut surface was coarsely granulated. Microscopic examination showed an increase in the connective tissue as well as periportal infiltrations of lymphocytes.

The pancreas evidenced a diffuse increase in the connective tissue.

In *the left orbit* the retrobulbar fatty tissue was replaced by greenish-yellow masses of tissue, filled with blood in some places. Under the microscope the tissue was seen to be extremely cellular, slightly fibrous and to contain numerous, relatively large cells with plentiful cytoplasm and a small nucleus. The cells frequently lay in small or large agglomerations. In some areas the cytoplasm was slightly stainable and somewhat granular; in others it was pale and smooth, In other sections there were numerous fibroblasts which infiltrated the agglomerations of cells mentioned earlier. Scattered giant cells were visible; they had one or several nuclei and the cytoplasm showed phagocytosis. There was plentiful substance showing an affinity for fat stains. Positive stainability for cholesterol was also present.

Nothing of particular interest was found in the other organs.

The autopsy thus afforded conclusive evidence in support of the diagnosis made on clinical grounds.

Comments

An account is given of a case of the Hand-Schüller-Christian disease presenting all the classical symptoms.

In view of the fact that a deposit of lipoids was the reason for which the disease was classified as a lipoidosis, it is remarkable that such deposits were found in only two organs in our case. This indicates that the deposits of lipoids are to be considered as secondary to some tissue injury and not due primarily to some disturbance in the lipoid chemistry, since those organs in which no deposits of lipoids were found were the site of severe pathological changes with an increase in the connective tissue and the presence of lymphocytes. One reservation, however, is if the original state has been changed by the cortisone therapy but the results of the biopsies before therapy still indicate the secondary nature of the lipoid deposits.

Cortisone therapy was instituted for the following three reasons:

1. The adrenocortical hormone plays a rôle in the metabolism of fats.

2. Satisfactory results have been obtained with the administration of the adrenocortical hormone or ACTH in other diseases involving the reticulo-endothelial system.

3. The adrenocortical hormone also has a generally stimulating effect on the tissues.

Summary

Report of an 1 $^1/_2$ year old boy with Hand-Schüller-Christian disease. A dose of 3 mg cortisone per kg of body weight per day, injected intramuscularly, initially resulted in conspicuous improvement. Thus, the general condition improved, the hepatomegaly and splenomegaly decreased, as did the protrusion of the eyeball, polyruia and polydipsia. Oedema subsequently developed and became increasingly severe; no changes were found in the blood chemistry to account for it. It was necessary to discontinue cortisone therapy after 3 weeks. The patient's condition deteriorated rapidly and he died after a further 5 days.

Un cas de maladie de Hand-Schüller-Christian traité par la cortisone.

Petit garcon agé 1 $^1/_2$ an. Une dose de 3 mg. de cortisone par kg. et par jour en injections intramusculaires, provoque initialement une amélioration visible. Ainsi, l'état général s'améliore, l'hépato splémomégalie régresse de même que l'exophtalmie, la polyurie et la polydipsie. Un œdème consécutif se développe et croît dans des proportions sévères; aucune modification dans l'examen chimique du sang n'a pu rendre compte de ce fait. Il fut nécessaire d'interrompre le traitement par la cortisone après 3 semaines. Le malade déclina rapidement et il mourut 5 jours plus tard.

Ein Fall von Hand-Schüller-Christian-Krankheit, mit Cortison behandelt.

Bericht über einen Fall bei einem anderthalbjährigen Knaben. Eine Dosis von 3 mg Cortison pro kg Körpergewicht und Tag, intramuskulär bewirkte anfänglich eine deutliche Besserung. Das Allgemeinbefinden besserte sich, Hepato- und Splenomegalie gingen zurück, ebenso die Protrusio bulbi, Polyurie und Polydipsie. Allmählich entwickelten sich Ödeme, die zunehmend schwerer wurden. Veränderungen im Blutchemismus konnten nicht gefunden werden. Eine Unterbrechung der Cortisontherapie war nach 3 Wochen notwendig geworden. Der Zustand des Patienten verschlimmerte sich schnell und der Tod trat nach weiteren 5 Tagen ein.

Un caso de enfermedad de Hans-Schüller-Christian tratado con cortisona.

Una dosis de 3 mg de cortisona por kilo de peso y día y por via intramuscular produjo inicialmente un espectacular resultado. El estado general mejoró la hepato-esplenomegalia disminuyó así como también la protrusión del glo ocular la poliuria y polidipsia. Se desarrolló subsiguientemente un edema que llegó a aumentar de un modo severo sin encontrar alteraciones hemoquimicas que lo justificaran. Fué necesario interrumpir la terapéutica con cortisona al cabo de 3 semanas. La enfermedad empeoró rápidamente muriendo el enfermito a los 5 días.

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Alkyl Mercury Poisoning

by

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Poisoning in adults from organic compounds of mercury has been reported with increasing frequency during the last decade. The symptomatology and the clinical picture have been described by HUNTER et al. and, in an earlier paper, by one of us (HERNER) and by AHLBORG and AHLMARK. Recently we observed 2 cases in infants, and as far as we know no similar cases have been recorded. As only the first case is definite, the data of this case will be described more fully.

Briefly the clinical picture in organic mercury poisoning in adults is dominated by symptoms due to severe damage to brain tissue; impaired vision, severe dysarthria, a spastic-ataxic gait, sometimes with inability to move at all, and an inability to get in touch with the environment. In spite of this there are no true signs of real mental retardation. Contrary to the findings in inorganic mercury intoxication there is as a rule no damage to parenchymatous organs.

Case Report: A male infant weighing 3,650 g at birth on 26th September 1947 and breast fed for the first 9 months was treated at the Pediatric Department from 17th Jan. until 19th September 1949. He could sit by himself at 8 months and could crawl and walk without help at 1 year. He was apparently healthy until the beginning of October 1948, when he developed a morbilliform rash accompanied by a short spell of fever. In the middle of October 1948 — the child then was about 13 months — the mother noticed that he showed no inclination to sit up and crawl about but preferred to remain lying. Afterwards he gradually became listless and clumsy; he seemed to become dull. He was admitted to the Pediatric Department on 17th Jan. 1949 on account of these observations.

On admission: Wt. 11,100 g. Age: 1 year and 4 months. Listless, slow reaction and offered no resistance to examination. Unable to get up or sit up without help. Slightly increased tonus of the left arm and the left leg. Movements fairly stereotyped. Unable to say a single word but burbled continuously. As far as intelligence was concerned, he gave the impression of a 7—8 months old child.

Neurologic findings: Reflexes of the biceps and triceps were more pronounced on the left side, the patellar reflexes were much increased, the reflexogenic zone was unusually large, and the Achilles' tendon reflexes were increased. Plantar reflexes were extensor. Ophthalmologic examination revealed nothing remarkable and the reactions of the pupils were normal.

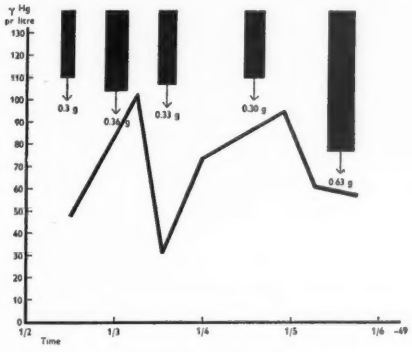
Laboratory findings: Cerebrospinal fluid was normal and the Wassermann reaction negative.

Roentgenograms of the skull showed nothing abnormal. The blood count was normal. *Electrocardiograms* on various occasions showed no changes. E.S.R. (by the method of Landau) was 19/26 mm on admission and remained increased for a long time; on discharge from hospital it was normal. Plasma protein: total protein 6.3 g per cent (alb. 4.6—glob. 1.7). On admission there was albuminuria and for some time afterwards the Esbach values were about 3 per millilitre. In the urinary sediment were a number of white and red cells as well as casts. N.P.N. was increased on a few occasions but afterwards normal as was the urinary sediment.

Inquiry into the family history revealed that the father had been treated for some time at the Medical Department, Lund, on account of mercury poisoning, and that he had afterwards been transferred to the Psychiatric Department. The family had used flour made from grain that had been treated with a preparation, panogen, containing organic mercury—an alkyl derivative—and this flour had been used for preparing porridge, of which the child had eaten on several occasions, probably almost daily, since he was about 9 months old. (Panogen is used by the farmers in seed dressing.)

Table 1.

Before starting the last series of BAL-injections the urine was examined for Hg. The result was 62 gamma/litre. Having finished the BAL-medication, which this time was rather strong, another sample of urine was tested in order to discover if more mercury could be mobilised by BAL, but the content was 58 gamma per litre, thus suggesting that further treatment would be of no value.



Examination of the urine for mercury showed a pathologic level of 48 gamma per litre. (These examinations were done at the State Institute for Public Health, Stockholm, by dr. R. Vesterberg).

As soon as mercury poisoning was diagnosed, the patient was given BAL (0,6 ml of a 10 per cent solution 6 times daily for 2 days and then 0.6 ml twice daily for 4 days with some modifications) during which time the urine was tested regularly for mercury (Table 1).

Despite long medication with BAL, urinary mercury persisted. In view of the long period of exposure this persistence was perhaps to be expected. Medication with BAL was therefore discontinued after treatment for 5 months with a total dose of almost 2 g BAL. The child left hospital on 19th Sept. 1949.

Except for a short initial spell of vomiting the general condition of the child was good throughout. Occasionally, however, he was remarkably restless and was sometimes difficult to feed. Now and then brief facial flushes were also noticed. During hospitalization the child increased 1.5 kg in weight. The neurologic signs persisted, the only difference being a slight abatement of the abnormally pronounced reflexes. The child was still unable to sit up or get up by himself when he left hospital. Mentally he was retarded on discharge and it is doubtful whether his mentality had developed at all during hospitalization. An *electroencephalogram* was

made on 27th July and the tracings were dominated by a frequency of 6 c.p.s. in all leads with some retarded spikes, which is no abnormal finding in children of this age. No focus, no paroxysms (dr. E. Nyman). The examiner was of the opinion that the dysrhythmia that might have been recordable in the acute stage had gradually subsided in spite of persistent clinical symptoms suggesting cerebral injury.

On admission there were also signs of renal injury which must be considered as being due to mercury poisoning. The albuminuria passed off and the urinary sediment became normal.

The mother, who showed urinary mercury output but no clinical symptoms (64 and 28 gamma per litre in 2 specimens collected in Febr. 1949), was delivered of an apparently healthy infant, a girl, who was kept under observation at the Pediatric Department for the first 2 months of life, during which time urinary examination revealed a mercury content of less than 3 gamma/litre. The infant showed no clinical signs of mercury poisoning at this time. Later on she has shown a marked mental retardation. She is unable to get up and can not sit up without support. Whether or not this mental and neurological state has the same etiology as that of her brother cannot be answered with certainty, but mercury intoxication, perhaps during early foetal life, seems to us to be a possible cause. The later course of the case will settle the definite diagnosis.

A follow-up examination of the family took place in May 1951. The girl had the same condition as described above but the boy showed an improvement with regard to his mental state. He was able to crawl, had a better contact with the environment, but was still to be considered as mentally retarded.

Discussion

The first infant presented the typical picture of chronic organic mercury poisoning with neurological signs fitting well with the syndrome as seen in adults. He also developed a disturbance of mental function with subsequent mental retardation. In addition there were signs of renal disease probably of the same type as in inorganic mercury poisoning, which, however, later disappeared. In chronic mercury poisoning in adults renal lesions are practically never seen. BAL was administered intensively. The disappearance of the renal lesions might have been due to this treatment. Examination of the amniotic fluid suggests that the placental barrier is impermeable to mercury, but the course of the second infant makes this opinion open to doubt.

It is improbable that the damage caused by organic mercury compounds is as closedly related to the action of the mercury ion as it is in sublimate poisoning, but in what way the *organic* mercury derivatives

are absorbed and later distributed in the body is not yet fully understood.

WARKANY and HUBBARD and later FANCONI and BOTSZTEJN among others reported several cases of acrodynia with urinary mercury responding favourably to medication with BAL. In most cases, however, it seems that the patients were suffering form *inorganic* mercury poisoning. In our patient vegetative symptoms reminiscent of Feer's disease were sometimes noticed, but otherwise the clinical picture and course of the disease differed considerably.

Summary

This paper describes a case of organic mercury poisoning in a child from a mercury-intoxicated family. The condition has not hitherto been reported among children. The child was poisoned after eating porridge prepared from flour which had been treated with an alkyl mercury compound, panogen, which is used by farmers in seed dressing. The main clinical signs and symptoms are due to severe damage to brain tissue, and thus differ from the parenchymatous lesions resulting from inorganic mercury poisoning. Treatment with BAL was of doubtful value.

Empoisonnement par un composé mercuriel organique.

Les auteurs décrivent un cas d'empoisonnement mercuriel organique chez un enfant d'une famille intoxiquée par le mercure. La maladie n'a pas été rapportée jusqu'ici chez des enfants. L'enfant fut intoxiqué après avoir mangé du porridge, préparé avec une farine, qui avait été traité avec un composé mercuriel organique, le panogen, utilisé par les fermiers dans le traitement du grain. Les signes et les symptomes cliniques de l'empoisonnement mercuriel organique sont dûs aux dommages sévères causés au tissu nervaux, et diffèrent donc des lésions parenchymateuses rencontrées dans l'intoxication mercurielle inorganique. Le traitement avec le BAL fut douteux.

Vergiftung mit einem organischen Quecksilberpräparat.

Die Autoren beschreiben einen Fall von organischer Quecksilbervergiftung bei einem Kind einer mit Quecksilber vergifteten Familie. Diese Krankheit ist bisher in der Literatur bei Kindern nicht beschrieben. Das Kind war nach dem Essen von Brei erkrankt, welcher aus Mehl hergestellt war, das mit einem Quecksilber-Alkyl, Panogen, behandelt worden war, wie es die Bauern zur Saatherrichtung verwenden. Die klinischen Zeichen einer organischen Quecksilbervergiftung sind durch einstere Schädigungen des Gehirngewebes hervorgerufen und dadurch unterscheiden sie sich von den Parenchymschädigungen bei nicht-organischer Quecksilberintoxikation. Die Behandlung mit BAL war zweifelhaft.

Intoxicación por mercurial orgánico.

Los autores describen un caso de intoxicación por un preparado mercurial orgánico en un niño de una familia intoxicada. La enfermedad no había sido hasta ahora en este tipo descrita en la literatura pediatríca. El niño se había intoxicado después de comer "porridge" preparado con harina la cual había sido mexclada con un compuesto mercurial orgánico — panogen — el cual es usado por los grangeros. Los signos y síntomas clínicos en la intoxicación mercurial por compuestos orgánicos son debidas a una afectación severa del tejido cerebral y en ello difiere de las lesiones parenquimatosas que se observan el na intoxicación mercurial por compuestos inorgánicos. El tratamiento con BAL es de éxito dudoso.

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Addendum

Since this paper was written we recently observed at the Pediatric clinic 4 other cases of alkyl mercury intoxication in children, which were all due to accidental poisoning with the same preparation for seed dressing as in the abovementioned report, panogen. All the patients have improved well without any sequelae so far. They have all left hospital. Two patients initially showed marked acute cerebral symptoms, excitement, dizziness and hallucinations and, in addition, fever. They were treated with BAL. In one of the patients there was a slight dysrhythmia of the electroencephalogram, but the other 3 failed to show any pathological findings. Examination of the urine for mercury revealed a mercury content of less than 3 gamma/litre in all 4 patients.

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BOOK REVIEW

C. GASSER: *Die hämolytischen Syndrome im Kindesalter.* 322 pages. George Thieme Publishers, Stuttgart.

The hemolytic anemias are attracting increasingly greater interest. Recognition of the importance of "blocking antibodies", study of the survival of transfused erythrocytes by means of differential agglutination and the use of improved methods for testing the osmotic and mechanical fragility of the erythrocytes, represent a few of the more important methods which have contributed to a better understanding of the underlying mechanisms.

In this new and clear monograph Dr. Gasser has given a very complete presentation of the hemolytic syndromes of childhood. The wealth of the material at the Fanconi clinic has enabled him to cover almost every type of hemolytic anemia with personal observations. In many cases interesting new findings have been added to the already known facts. It is natural that the chapter on Rh-immunization in the newborn is dealt with in detail, comprising no less than 56 pages. In other sections the reactions following mismatched transfusions and other hemolytic mechanisms due to immune reaction are given in full detail. The "inclusion body anemia" of premature children is a Swiss speciality of which the mechanism has still to be explained.

Amongst the constitutional hemolytic anemias, the microspherocytosis and the Thalassemia are presented in detail and a lot of other types, also including those of very recent recognition, are discussed as well. The list of authors is very extensive, comprising about 1 000 references. The photographic illustrations are good and the graphic presentations of many of the cases are exceedingly clear. This book will certainly find numerous readers not only amongst pediatricians and hematologists.

Bo Vahlquist, Uppsala.

WILHELM KÜNZER: *Über das Blutfarbstoffwechsel gesunder Säuglinge und Kinder. Mit besonderer Berücksichtigung der Anämisierungsvorgänge im Verlauf des 1. Trimenons.* S. Karger, Basel, Schweiz. Price SFr 11.—.

There has been much discussion about the "physiologic" anemia which develops during the first months of life. Opinions about the mechanism of this anemia have varied considerably as have opinions on the magnitude of reduction of hemoglobin. The big question has been: decreased erythropoesis or increased destruction of red blood corpuscles.

The author has tried to elucidate these questions making a study of the hemoglobin metabolism. The erythropoesis has been evaluated by counting the reticulocytes. The total amount of circulating hemoglobin has been calculated and the amount of fetal hemoglobin has been determined.

As the result of quantitative analysis of urobilin in urine and faeces and bilirubin in faeces the author has been able to determine the degree of blood destruction. Bilirubin in faeces has been analyzed by a new method, devised by the author.

The figures show that the hemoglobin balance is positive during the first week of life but afterwards becomes negative. There is a marked increase of destruction of hemoglobin up to the 8th—10th week when half of the amount of hemoglobin present at birth has been lost. This is said to be the result of a rapid destruction of fetal hemoglobin. After the 10th week of life destruction of hemoglobin takes place at a slower speed, even slower than in adults and this is explained by a longer life span of the erythrocytes.

Methods employed in this investigation are not very exact and it is doubtful if the results can form the basis for any definite conclusions. The excretion of urobilin and bilirubin cannot be considered as a quantitative measurement of hemoglobin breakdown; at least this does not hold in the newborn infant, where bilirubin will be deposited in the tissues to a certain extent.

Calculating hemoglobin metabolism the author has determined the total amount of circulating hemoglobin. Plasma volume has been determined with Congo red or Periston and total hemoglobin has then been calculated on the basis of hematocrit and g per cent hemoglobin. There are many errors in this method. Plasmavolume has only been determined in a few cases (9 children during the first three months). Each child has only been examined over a short period of time, as a rule 1—2 weeks and only in a few cases repeatedly from birth to 3 months of age. It seems that it would have been wise to examine each child repeatedly during the first 3 months. This is especially true when the material is small. There are only 6 to 12 cases in each age group.

The results differ from other new investigations, where it has been shown that "physiologic" anemia is the result of dilution of the blood. Nor do they conform either with the results of Mollison. Studying life span with the method of differential agglutination Mollison has been able to prove that adult erythrocytes have a normal life span if transferred to newborn infants and that fetal erythrocytes (from placenta) have almost the same life span. This is an argument against an increased destruction of erythrocytes in the newborns.

Bengt Jonsson, Stockholm.